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THE SIXTH FRAMEWORK PROGRAM
AND THE EUROPEAN RESEARCH AREA

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As stressed in the European Commission’s January 2000 Communication “Towards a European Research Area”, the Sixth Framework Program will be one of the most important instruments to implement the European Research Area. The Commission’s proposals for the Sixth Framework Program follow on from the Guidelines of the Commission’s 2000 communication and are based on the preliminary conclusions of the debate in the European Parliament, the Council and other institutions, taking also into account the views expressed by the member states, the scientific community and industry. The Sixth Framework Program will be structured around three targets: integrating research, structuring the European Research Area, and strengthening the foundations of the European Research Area.

The activities carried out to further this objective, which will represent the bulk of the efforts deployed under the framework program, are intended to integrate research efforts and activities on a European scale. They will be carried out in a limited number of priority thematic areas. Seven priority areas have been selected:

- genomics and biotechnology for health;
- information society technologies;
- nanotechnologies, intelligent materials, and new production processes;
- aeronautics and space;
- food safety and health risks;
- sustainable development;
- citizens and governance in an open European knowledge-based society.

The activities carried out under this heading will complement research within the thematic priority areas of research and comprise the following:

- anticipating the EU’s scientific and technological needs;
- specific research activities for small and medium enterprises;
- joint research center activities;
- specific international cooperation activities;
- scientific and technological cooperation activities carried out in the whole field of science and technology, in particular the cooperation activities of COST and the European Science Foundation;
- actions to encourage transregional cooperation regarding innovation and support for the setting up of technology businesses, as well as for the preparation of regional and transregional strategies in this area;
- actions to experiment with new tools and new approaches concerning technological innovation;
- establishment or consolidation of information services, in particular electronic services, and assistance services relating to innovation (technology transfer, protection of intellectual property, access to risk capital);
- economic and technological intelligence activities (analyses of technological developments, applications and markets, and processing and dissemination of information which may help researchers, entrepreneurs, in particular SMEs, and investors in their decision-making);
- analysis and evaluation of innovation activities carried out in the framework of Community research projects and exploitation of lessons that can be learned from innovation policies.

The target of strengthening the foundations of the European Research Area will be achieved by simplifying and streamlining the implementation arrangements on the basis of the intervention methods defined and the decentralized management procedures envisaged. These activities will be carried out around four main areas: research and innovation, human resources and mobility, research infrastructures, and science/society.

Making a reality of the European Research Area depends first and foremost on improving the coherence and coordination of research and innovation activities and policies conducted at national, regional and European levels. Action by the Community can help to promote efforts to this end and lay the foundations in terms of the information, knowledge and analyses that are essential for the successful completion of this project. These activities, to be carried out in the whole field of science and technology, will take the following forms: to step up the coordination of research activities carried out in Europe at both national and European levels, financial support will be considered for:

- the mutual opening up of national programs;
- networking of research activities conducted at national levels;
- scientific and technological cooperation activities carried out in other European cooperation frameworks, in particular the cooperation activities of COST and the European Science Foundation;
- collaboration and joint initiatives of specialized European scientific cooperation organizations; efforts will be made to encourage European coordination of research activities across the range of research priorities, including:
  - health: health issues in specific population groups (in particular children and the aged population); major diseases and disorders (for example, diabetes and hepatitis);
  - environment: sustainable local and urban development; seismic risks;
  - energy (fossil fuels): new-generation power plants (“near-zero emission”), energy storage, transport and distribution.

These actions will be implemented in the general context of efforts undertaken to optimize the overall performance of European scientific and technological cooperation and ensure that its different components, including COST and Eureka, complement each other. In order to support the coherent development of research and innovation policies in Europe, analyses and studies will be carried out as well as work relating to scientific and technological foresight, statistics and indicators. Moreover, a great effort will be made to ensure:
– support for the operation of specialized working groups and forums for concerted action and political debate;
– support for work on the benchmarking of research and innovation policies at national, regional and European levels;
– support for carrying out work on the mapping of scientific and technological excellence in Europe;
– support for carrying out the work needed to improve the regulatory and administrative environment for research and innovation in Europe.

What about the distribution of research funds in Italy? Are Italian researchers supported in building excellence networks and cooperation programs with other European institutions? Italian universities and young researchers need strong external support in order not to be ruled by industrial interests: there is a need for a research network in the field of medicine and health care, based on innovation and real development.

There is a great need for an Italian Agency of European Research, dedicated to promote and coordinate national and international research programs, to support scientific and research activities of major relevance for the national system, and to facilitate the development of academic research by joining and coordinating Italian universities so that they can carry out research activities in pursuit of excellence and strategic relevance both at a national and international level, in the framework of European cooperation and integration.

The Agency must promote the valorization, the precompetitive development and the technological transfer of research results attained by its own scientific network and by third parties with whom cooperation relationships have been established. And, last but not least, it must promote collaboration in the fields of science, technology and technical regulations with organizations and institutions of other countries, and with supranational organizations in the context of extragovernmental agreements. The Agency must participate in international research centers, in collaboration with analogous scientific institutions of other countries. To do so, specific skills for the participation of Italy in organizations or international scientific programs of an intergovernmental nature must be provided.

PROGNOSTIC AND THERAPEUTIC IMPACT OF SENTINEL NODE MICROMETASTASIS IN PATIENTS WITH INVASIVE BREAST CANCER

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Abstract

Aims and background: Locoregional lymph node status is one of the most important prognostic factors determining the need for adjuvant chemotherapy in patients with breast cancer. Many authors have reported that micrometastases were not detected by routine sectioning of lymph nodes but were identified by multiple sectioning and additional staining. Among lymph node-negative patients 15–20% had an unfavorable outcome at five years from primary surgery. Sentinel lymph node (SLN) biopsy is an accurate technique for identifying axillary metastases because the pathologist utilizes hematoxylin-eosin (H-E) staining together with immunohistochemistry (IH) to examine all lymph node sections. Sentinel node micrometastasis has therefore become an important tumor-related prognostic factor. Methods and study design: From November 1997 to October 2001 we examined in 210 patients the pathological features of primary breast lesions and SLN metastases and we correlated these with the tumor status of non-SLNs in the same axillary basin. We applied IH examination to both SLNs and non-SLNs of patients who were negative for metastasis by standard H-E examination. Results: In this study lymph node staging was based on SLN findings, primary tumor size, and the presence of peritumoral lymphovascular invasion (LVI). We found 18 SLN micrometastases (9%) in 210 patients and one of these (5.5% of patients with SLN micrometastasis) also had one non-SLN metastasis: this patient had LVI and a larger primary tumor than patients with SLN micrometastasis without non-SLN metastasis. We also found 24 SLN macrometastases (11.5%) in 210 patients and 13 of these (54.2% of patients with SLN micrometastases) had one or more non-SLN metastases. Conclusions: According to the results reported in the literature, tumor cells are unlikely to be found in non-SLNs when the primary lesion is small and SLN involvement micrometastatic (5.5% in our experience, 7% in Giuliano’s). Our findings suggest that axillary lymph node dissection may not be necessary in patients with SLN micrometastasis from T1 lesions.

Key words: breast cancer treatment, micrometastasis, sentinel node.

Introduction

In order to plan adjuvant therapy in patients with invasive breast cancer, we must consider two kinds of factors: prognostic factors (able to define the risk of recurrence) and predictive factors (able to show the activity of specific adjuvant therapies)1. Among the prognostic factors locoregional lymph node status is the most important, but there are also biological parameters which are important to define neoplastic cell growth (Ellis-Elston cellular grading, percentage of hormonal receptors, Her2-neu and p53)2. The prognosis of these patients depends on the presence or absence of locoregional lymph node metastases and, although, depends on number of locoregional metastatic lymph nodes. Among node-negative patients 25%-35% have a bad prognosis: many authors have described various correlated indexes (eg size and biological features of the primary tumor), but locoregional lymph
Discussion

The prognostic relevance of the presence of SLN micrometastases shown by IH or molecular methods is not clear. Many authors carry on the adverse prognostic of SLN micrometastasis similar to SLN macrometastasis; according to when we find SLN micrometastasis we must perform adjuvant therapy according to standard treatment schedules. We therefore do not think it is appropriate to downstage the primary breast lesion in the presence of micrometastases, with a consequent decrease in the percentage of N0 patients and change of prognosis. Two different types of SLN micrometastasis should be distinguished: 1) capsular or subcapsular micrometastasis, carrying a better prognosis, and 2) nodal micrometastasis, carrying a worse prognosis. The latter type of micrometastasis always taked with peritumoral vascular invasion and bone marrow micrometastasis.

The association of SLN micrometastasis with non-SLN metastases is uncommon (7% in Giuliano’s experience, 5.5% in ours); primary tumor size, type of SLN micrometastasis and peritumoral vascular invasion are very important prognostic factors. In our opinion patients with T1 breast tumors and capsular or subcapsular SLN micrometastasis without peritumoral vascular invasion can be spared axillary lymph node dissection.

Results

We studied a number of prognostic parameters to stage the primary breast tumors: tumor size (T), peritumoral vascular invasion, presence of micro- or macrometastasis, and type of micrometastasis. We identified 18 SLN micrometastases (9%) in 210 patients: one of these (5.5%) of patients with micrometastatic SLNs also had a metastasis in a non-SLN; this patient had a primary tumor larger than 2 cm, peritumoral vascular invasion and bone marrow micrometastasis.

The other patients (94.5%) with primary tumor larger than 2 cm, peritumoral vascular invasion and SLNs also had a metastasis in a non-SLN; this patient had an internal mammary chain (IMC) drainage. The association of IMC drainage is not a routine procedure would demand complete axillary lymph node dissection.

Material and methods

From November 1997 to October 2001 we studied the histopathological features and biological parameters of 210 breast cancer patients (T1N0M0); we also assessed the presence of metastases in excised SLNs. Each locoregional lymph node was examined by H-E staining and IH. The mean dimension of the primary breast tumors was 1.3 cm (range 0.5-3 cm); for this reason we mainly performed breast-conserving surgery (97 quadrantectomies (46%) and 54 ROLL (radio-guided occult lesions localization) (26%) compared to mutilating surgery (59 Patey’s modified mastectomy (28%).

References


SURALINE NODE BIOPSY IN THE EVALUATION OF THE INTERNAL MAMMARY NODE CHAIN IN PATIENTS WITH BREAST CANCER

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Abstract

Aims and background: In patients with breast cancer the presence of internal mammary chain (IMC) metastases changes tumor staging, and the occurrence of IMC drainage is quite common in breast cancer. Nevertheless, IMC dissection is not a routine pro-
procedure in modern surgical approaches towards breast cancer. We therefore need minimally invasive techniques for accurate assessment of the IMC nodal basin. The aim of this study was to investigate whether sentinel node biopsy (SLN) could offer a solution. Methods and study design: From November 1997 to June 2001 143 female patients who were eligible for breast cancer surgery were included in the study. All patients had T1 breast cancer and clinically negative axillae. Patients were submitted to preoperative lymphoscintigraphy with subsequent SLNB. We used a 99m-technetium nanocolloid tracer (Nanocoll®) that was injected peritumorally so as to have about 10 MBq of radioactivity at the time of surgery. Scintigraphy was performed about 17 hours after tracer administration. During surgery, lymphoscintigraphic imaging and a gamma ray detection probe were used to locate the sentinel node. Histological examination after embedding in paraffin was usually requested and multilevel sectioning of the sentinel node (SLN) was performed, with hematoxylin and eosin staining and immunohistochemistry. Results: Preoperative lymphoscintigraphy localized SLNs in the IMC basin in 27 of 143 patients (18.9%). Harvesting of IMC-SLNs based on lymphoscintigraphy results was successful in 20 of 27 patients (74.1%). Histological examination revealed micrometastases in four of the 20 harvested nodes. One of these patients showed no axillary drainage and no axillary lymph node dissection was therefore performed. In the remaining three patients also axillary SLNs were harvested, which turned out to be free from metastatic involvement. Conclusions: In our experience lymphoscintigraphy with SLNB was an accurate method to detect IMC metastases in patients with breast cancer. We recommend peritumoral tracer injection and a reasonable interval between injection and scintigraphy. IMC-SLN biopsy did not result in any serious additional complications or morbidity. In our study this approach led to improved cancer staging: four of 20 harvested IMC-SLNs proved to be micrometastatic. None of these four patients had metastatic axillary SLNs. Exclusive drainage to the IMC is present in only a small number of breast cancer patients, and our results suggest that it is possible to avoid unnecessary axillary node dissection in such cases.

Key words: breast cancer, internal mammary chain, radioguided surgery, sentinel node biopsy.

Introduction

Lymph node metastases to the internal mammary chain (IMC) may occur in patients with breast cancer, and knowledge of IMC involvement may alter patient management. The presence of IMC metastases changes tumor staging, since IMC metastases are an important independent prognostic factor. These patients should undergo systemic adjuvant hormonal therapy and chemotherapy; subsequent irradiation of the metastatic IMC nodes may be appropriate for local disease control.

Although IMC drainage is quite common in breast cancer, IMC dissection is not a routine procedure in modern surgical approaches. Nevertheless, staging that is limited to the status of the axillary lymph nodes may lead to understaging of a considerable number of patients. Minimally invasive techniques are required for accurate assessment of the IMC nodal basin. Sentinel node biopsy (SLNB) with preoperative lymphoscintigraphy after peritumoral radiotracer injection may represent a reliable technique for assessing the IMC status of patients with breast carcinoma.

Material and methods

Patients

From November 1997 to June 2001 143 patients were enrolled in the study. All patients were women; their median age was 61 years (range, 43-80 years). Patients had mammographic or ultrasonographic evidence of T1 breast cancer. Malignancy (infiltrating carcinoma) was confirmed in all of them by histological examination of the tumor specimen. The axilla was clinically negative in all cases. Patients were submitted to preoperative lymphoscintigraphy with subsequent SLNB.

Lymphoscintigraphy

In the afternoon before surgery a nanocolloidal tracer (Nanocoll®, Nycomed Amersham Sorin, Saluggia, Italy) with an average particle size of less than 80 nm was injected. Nanocoll® was labeled with technetium-99m; we injected an average dose of 130 MBq (range, 110-150 MBq) peritumorally so as to have about 10 MBq of radioactivity at the time of surgery. The administered volume was 0.3-0.4 cc. In patients with palpable breast lesions tracer administration was performed under touch control; in the case of non-palpable lesions we used sonographic or stereotactic guidance (depending on the imaging features of the tumor).

We performed scintigraphy the morning of surgery, about 17 hours after tracer administration. Anterior and lateral projections were obtained using a large-field-of-view gamma camera. Breast-conserving surgery was performed in all patients but 13 with centrally located tumors.

A gamma ray detection probe (Scintiprobe mr 100®) with lymphoscintigraphic imaging was used intraoperatively to locate the sentinel node and to guide its surgical removal. Histological examination after embedding in paraffin was usually requested, and multilevel sectioning of the sentinel node (SLN) was performed, with hematoxylin and eosin staining and immunohistochemistry.

Results

Preoperative lymphoscintigraphy detected SLNs in the IMC basin in 27 of 143 patients (18.9%). Eighteen of these 27 patients (66.7%) had at least one SLN in the axillary basin too, while only IMC drainage was present in nine patients (33.3%, 6.3% of all patients). IMC-SLN harvesting based on the results of lymphoscintigraphy was successful in 20 of 27 patients (74.1%). Attempts at surgical excision failed in seven cases where the SLNs were located under a rib. In one patient we caused a small pleural lesion, but this had no consequences and no particular care was required.

Histological examination revealed micrometastatic involvement of four of the 20 harvested IMC nodes. One of these four patients showed no axillary drainage and therefore no axillary lymph node dissection was performed. The remaining three also had axillary SLNs. The axillary SLNs were harvested but proved to be free of metastatic involvement in all cases.

Primary tumor location in the 27 patients with IMC drainage was:
- lower outer quadrant, twelve patients;
- upper inner quadrant, six patients;
- upper outer quadrant, five patients;
- lower inner quadrant, four patients.

In 17 patients (63%) the tumors were located in the outer quadrants and in ten patients (37%) in the inner quadrants.

Discussion

It is still being debated in the literature whether lymphoscintigraphy with SLNB is an accurate method for the detection of IMC metastases in patients with breast cancer; however, we think it is a reliable technique to examine the IMC basin. High-quality lymphoscintigraphy allows accurate mapping of lymphatic drainage. We have a couple of recommendations in
RADIOLABELED LOCALIZATION OF THE SENTINEL LYMPH NODE: DOSIMETRIC EVALUATION IN PERSONNEL INVOLVED IN THE PROCEDURE

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Abstract

Aims and background: Peritumoral injection of 99mTc-labeled colloids for lymphoscintigraphy and radioguided surgery does not entail any relevant radiation burden to the patients. The real issue about radiation protection concerns the personnel involved in the procedure besides the nuclear medicine personnel. The aim of our study was to evaluate the cumulative doses to personnel involved during the injection of radiolabeled compounds under ultrasonic or stereotactic guidance and the radiation burden to the personnel involved in the surgical incision of the tumor 24 hours after the administration of 99mTc-labeled colloids. Methods and study design: We performed environmental contamination tests (SMEAR TEST) and exposure evaluation in the operating room. Results: In the operating room the removed activity in the sampled analysis was less than 0.5Bq/g and exposure to the personnel was less than 6µSv/h. The evaluations made during ultrasound guidance demonstrated an equivalent and effective dose less than 20µSv. Conclusions: Our results show that during ultrasound or stereotactic administration of radiolabeled compounds the radiation burden to the personnel involved in the procedure is virtually negligible. The surgeons too are exposed to a negligible radiation dose.

Key words: dosimetry, lymphatic mapping, radioprotection, 99mTc-labeled colloid.

Introduction

The standard procedure for the evaluation of axillary nodal involvement in patients with breast cancer is still complete lymph node dissection. However, about 70% of patients are found to be free from metastatic disease. Lymphatic mapping and sentinel lymph node (SLN) biopsy are changing this situation, reducing the morbidity of surgical treatment and improving staging of the axillary lymph node basin.3,4

Peritumoral injection of 99mTc-labeled colloids for lymphoscintigraphy and radioguided surgery is usually reported to co-exist with axillary node metastases. This is an important finding because in the literature IMC metastases are usually found to have metastatic axillary SLNs. Even if the outer breast quadrants would not be expected to have significant drainage to the IMC, tumors in any portion of the breast may drain to this nodal basin.10-13 This applies for both non-palpable lesions and sentinel node localisation.4

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Key words: dosimetry, lymphatic mapping, radioprotection, 99mTc-labeled colloid.

Introduction

The standard procedure for the evaluation of axillary nodal involvement in patients with breast cancer is still complete lymph node dissection. However, about 70% of patients are found to be free from metastatic disease. Lymphatic mapping and sentinel lymph node (SLN) biopsy are changing this situation, reducing the morbidity of surgical treatment and improving staging of the axillary lymph node basin.3,4
phosphoroscinography and radioguided surgery does not entail any relevant radiation burden to patients. The real issue about radiation protection in radioguided surgery concerns the personnel involved in the procedure besides the nuclear medicine personnel.

The aim of our study was to evaluate the cumulative doses to personnel involved in this procedure during the injection of radiolabeled compounds under ultrasound or stereotactic guidance. In addition, we wanted to evaluate the radiation burden to the personnel involved in the surgical incision of the tumor, 24 hours after the administration of 99mTc-labeled colloids.

Materials and methods

Between October and December 2000 we studied seven patients with breast cancer. We excluded from our population patients with palpable axillary lymph nodes, patients with tumors with a diameter of >2.5 cm, patients with multifocal or multicentric cancer, pregnant patients and patients older than 80 years. All patients underwent surgical incision the day after administration of 18.7 MBq of 99mTc-nanocolloid (mean size 80 nm) in a volume of 0.5 mL. We used a 22G needle for the injection; in all cases radiolabeled colloids were administered peritumorally (in six cases under ultrasound guidance, in one case under stereotactic guidance). After administration of 99mTc-nanocolloid all patients underwent lymphoscintigraphy. We acquired static anterior and lateral views to locate the SLN, which was marked on the skin.

In order to assess the radiation protection issues during 99mTc-nanocolloid administration we performed environmental contamination tests (SMEAR TEST) and exposure evaluation in the operating room. The samples obtained with the SMEAR TEST were analyzed using germanium detectors with a multichannel analyzer.

At the same time we measured the equivalent and effective dose to personnel involved in ultrasound guidance. For our measurements we utilized film badges and thermoluminescent dosimeters (TLD) for hands and fingers. In two cases we repeated the same tests and exposure measurements the day after injection of the radiolabeled compounds, during the surgical incision.

Results

In the operating room the removed activity in the analyzed samples was always less than 0.5Bq/g and the exposure of the personnel was less than 6µSv/h. The evaluations made during ultrasound guidance demonstrated an equivalent and effective dose less than 20µSv (threshold of the measurement system).

Discussion and conclusions

The use of radioactive compounds in clinical practice must be justified by the advantages to the patient; however, the risks for the personnel involved in the procedure must be reasonable. Investigators at many cancer centres have confirmed that the SLN is the first lymph node to receive lymphatic drainage from a primary breast cancer and therefore the lymph node most likely to contain metastatic tumor cells. The tumor status of the SLN should accurately predict the histopathological status of the regional lymphatic basin draining the tumor; in particular, a metastasis-free SLN would exclude tumor spread to the regional lymphatic basin at risk.

As shown by our results, during ultrasound or stereotactic administration of radiolabeled compounds the radiation burden to the personnel involved in the procedure is virtually negligible. Surgeons too are exposed to a negligible radiation dose because the doses injected are very low and two or three physical half-lives elapse between tracer injection and surgical procedure.

These two factors explain the results obtained in a carefully controlled study based on 50 SLN biopsy procedures and 50 radioguided procedures involving intratumoral injection of 99mTc-albumin macroaggregates, which are permanently retained at the injection site (about 11 MBq (300 µCi) in both cases).

According to the review article by Paganeli and coworkers, the cumulative doses to personnel involved in the procedure (surgeons, nurses, pathologists) for 100 operations corresponded at most to about 1% (mean absorbed dose) or about 10% (mean effective dose) of the annual dose limits for the general population. The same authors reported that radioactivity counted in operating room materials possibly contaminated during surgery was also minimal and did not require any special handling procedures. These data are consistent with those obtained by other groups.

In conclusion, our data and those from other centers confirm that radioguided procedures are safe for the personnel involved.

References

Preliminary study of sentinel node identification with 99mTc colloid and blue dye in patients with endometrial cancer

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Abstract

Aims and background: Intraoperative lymphatic mapping and sentinel node (SLN) biopsy have generated a tremendous amount of interest and are already established as part of the standard practice in the surgical management of breast cancer and melanoma. To reduce extensive radical procedures and decrease the morbidity in the treatment of gynecologic malignancies, much effort is being made to use less aggressive interventions. The purpose of our study was to determine the feasibility of SLN mapping in a group of patients with endometrial cancer at early stages. Method and study design: Between September 2000 and May 2001 11 patients with endometrial cancer FIGO stage Ib (n = 10) and Ia (n = 1) underwent laparoscopic SLN detection during laparoscopy-assisted vaginal hysterectomy with bilateral salpingo-oophorectomy and bilateral systematic pelvic lymphadenectomy. Radioactive isotope injection was performed 24 hours before surgery and blue dye injection was performed just before surgery in the cervix at 3, 6, 9 and 12 hours. A 350 mm lar- paroscopic gamma scintiprobe MR 100 type 11, 99mTc settled (Pol Hi Tech), was used intraoperatively for SLN detection. Results: Seventeen (17) SLNs were detected with lymphoscintigraph- hy (six bilateral and five unilateral). At laparoscopic surgery we found the same locations belonging at internal iliac lymph nodes (the so-called Lebeuf-Godard area, lateral to the inferior vesical artery, ventral to the origin of the ureter artery and medial or caudal to the external iliac vein). Fourteen (14) SLNs were negative on histological analysis and three were positive for micrometastases (mean SLN sections = 60). All other pelvic lymph nodes were negative at histological analysis. The same SLN locations detected with the gamma scintiprobe were observed at laparoscopy after patent blue dye injection. Conclusions: Our pre- liminary data suggest that combined 99mTc-labeled colloid and vi- tal blue-dye techniques are feasible for SLN detection in endometrial cancer; they represent a very promising tool to trans- fer the most likely lymph node to contain metastatic tumor cells. The methods to identify such nodes are staining with iso- sulfan blue dye and/or detection of the uptake of a radionuclide that spreads the same way as lymph through the lymphatics. However, the successful identification of the SLN(s) is only the first step, because it is necessary to examine these nodes histopathologically and immunohistochemically for an accurate identification of (micro)metastases. The histological status of this node is expected to be representative of the remaining lymph nodes, ie, a histologically negative SLN would predict the ab- sence of tumor spread into “non-sentinel” lymph nodes. SLN detection may therefore prevent unnecessary, extensive lymph node dissection.

Radical hysterectomy with pelvic lymphadenectomy is the most commonly performed definitive surgical procedure for pa- tients with FIGO stage Ib and Ia endometrial cancer. However, similarly to early-stage breast cancer, only few of these patients have pelvic lymph node metastases, while many patients who undergo radical lymph node dissection suffer from side effects after surgery. To reduce the number of extensive radical proce- dures and decrease the morbidity in gynecologic malignancies, much effort is being made to perform less aggressive interven- tions. In tumors that drain to deep pelvic lymph nodes, such as endometrial cancer, SLN detection has not been proved feasible yet. The aim of our study was to determine the feasibility of SLN mapping in a group of patients with early stage endometrial cancer to possibly reduce unnecessary radical lymph node dissec- tion.

Patients and methods

Between September 2000 and May 2001 11 patients with FIGO stage Ib (n = 10) and Ia (n = 1) endometrial cancer underwent laparoscopic SLN detection during laparoscopy-assisted vaginal hysterectomy with bilateral salpingo-oophorectomy and bilateral systematic pelvic lymphadenectomy. The day before surgery all patients underwent lymphoscintig- raphy after administration of 99mTc-nanocolloid into the cervix at 3, 6, 9 and 12 hours. Scintigraphic images were obtained with a gamma camera (GE 400T) equipped with a general purpose colli- mator; the acquisition window was set at 140 KeV. For static pla-nar images the matrix size was 256x256; we acquired static ante- rior and lateral views to locate the SLN. A 350 mm laparoscopic gamma scintiprobe MR 100 type 11, 99mTc settled (Pol Hi Tech), was used intraoperatively for SLN detection. For visual detection of the SLN vital blue dye was injected at the start of surgery.

Results

Seventeen SLNs were detected at lymphoscintigraphy (six bi- lateral and six unilateral). At laparoscopic surgery we found the same locations belonging at internal iliac lymph nodes (the so-called Lebeuf-Godard area, lateral to the inferior vesical artery, ventral to the origin of the ureter artery and medial or caudal to the external iliac vein). Fourteen SLNs were negative at histological analysis and three proved positive for micrometastases (mean SLN sections = 60). All other pelvic lymph nodes were negative at histological analysis. The same SLN locations detected with gamma scintiprobe were observed during laparoscopy after patent blue dye injection.

Discussion

Quality of life has become a very important issue in deciding the extent of surgical procedures for patients with different types of cancers. In recent years, more attention has been paid to pre- serving organ function and cosmesis.
The concept of sentinel lymph node identification and lymphatic mapping is established as part of the standard practice in the surgical management of breast cancer and melanoma. Investigators identify SLNs by combining radioactive tracers and blue dyes. In the past decades retroperitoneal lymph node dissection has been included in most surgical protocols for gynecologic oncology. Today, its usefulness is questioned. Recent studies on cervical, ovarian and endometrial cancer have attempted to redefine the role of retroperitoneal lymph node dissection. Despite these studies, it appears obvious that dissection has a minor impact on survival while it increases the surgical morbidity. The immediate goals today would be to target and remove only the necessary lymph nodes and to decrease the morbidity associated with the procedures. To reach these goals, two new approaches are currently under investigation: laparoscopic dissection and sentinel lymph node identification.

In the present preliminary study we evaluated the combination of preoperative lymphatic mapping with intraoperative probe detection in stage Ib and IIa endometrial cancer. In this series of 11 patients SLNs were found only in the internal iliac area and none of the patients with histologically negative SLNs had metastases in other pelvic lymph nodes (negative predictive value 100%).

Our findings demonstrate that preoperative lymphatic mapping is an easy technique to visualize the SLN in endometrial cancer. The sentinel lymph node status may be representative of the pelvic lymph node status in endometrial cancer and treatment of women suffering from this cancer could thus be modified to a less radical approach; in fact, in the present series all women in whom lymph node dissection could be avoided were identified.

In conclusion, our preliminary data suggest that in endometrial cancer combined 99mTc-labeled colloid and vital blue-dye techniques are feasible, and they represent a very promising tool to mitigate the management of early stage endometrial cancer. However, studies involving larger patient series will be required to establish the role of sentinel lymph node detection in endometrial cancer for further therapy concepts and planning.

References

SENTINEL NODE DETECTION IN BREAST CARCINOMA

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Abstract

Aims and background: The standard procedure for the evaluation of axillary nodal involvement in patients with breast cancer is still complete lymph node dissection. However, about 70% of patients are found to be free of metastatic disease while axillary node dissection may cause significant morbidity. Lymphatic mapping and sentinel lymph node (SLN) biopsy are changing this situation. Methods and study design: In a period of 18 months we studied 201 patients with breast cancer, excluding patients with palpable axillary nodes, tumors >2.5 cm in diameter, multifocal or multicentric cancer, pregnant patients and patients over 80 years of age. Before surgery 99mTc-labeled colloid and vital blue dye were injected into the breast to identify the SLN. In lymph nodes dissected during surgery the metastatic status was examined by sections at reduced intervals. Only patients with SLNs that were histologically positive for metastases underwent axillary dissection. Results: We localized one or more SLNs in 194 of 201 (96.5%) patients; when both techniques were utilized the success rate was 100%. Histologically, 21% of patients showed SLN metastases (7.8% micrometastases) and 68% of these had metastases also in other axillary nodes. None of the patients with negative SLNs developed metastases during follow-up. Conclusions: At present there is no definite evidence that negative SLN biopsy is invariably correlated with negative axillary status; however, our study and those of others demonstrate that SLN biopsy is an accurate method of axillary staging.

Key words: breast cancer, lymphatic mapping, sentinel node biopsy, staging. 99mTc-labeled colloid.

Introduction

The current standard of surgical care for patients with invasive breast cancer is complete removal of the tumor by mastectomy or lumpectomy, with documentation of negative margins, followed by complete axillary lymph node dissection (ALND) defined as dissection of levels I, II and III. In fact, the status of axillary lymph node remains the single most important independent prognostic variable. However, routine performance of ALND in stage
I and II breast cancer has become controversial because about 70% of patients are found to be free of metastatic disease while ALND can potentially lead to significant morbidity.\(^2\) Approximately 40% of patients treated with complete ALND develop acute lymphedema, and 5-10% develop chronic lymphedema. The limitation of axillary dissection to level I and II has not changed the incidence of acute lymphedema, while the incidence of chronic lymphedema has decreased to 5%.\(^3\)\(^,\)\(^4\) Other significant complications of ALND can be paresthesia due to costobrachial nerve injury, wound infection, seroma formation and drain complications.

Lymphatic mapping and sentinel lymph node (SLN) biopsy are rapidly supplanting complete ALND as the axillary staging procedure of choice in the treatment of breast cancer; this minimally invasive procedure may reduce the morbidity of surgical treatment and improve staging of the axillary lymph node basin.\(^5\) In our center we have avoided performing ALND in patients with early stage breast carcinoma since March 2000; in this study we report our results.

**Materials and methods**

In a period of 18 months we studied 201 patients with breast cancer. We excluded from our population patients with palpable axillary lymph nodes, patients with tumors \(>2.5\) cm in diameter, patients with multifocal or multicentric cancer, pregnant patients and patients over 80 years of age.

The day before surgery patients underwent lymphoscintigraphy after administration of \(99m\)Tc nanocolloid. Scintigraphic images were obtained with a gamma camera (GE 400T) fitted with a general-purpose collimator; the acquisition window was set at 140 Kev. For static planar images the matrix size was \(256 \times 256\); we acquired static anterior and lateral views to locate the SLN, which was marked on the skin. On the day of surgery, just before the incision an injection with blue dye was administered.

We studied 97 patients with both techniques, while 25 patients were studied only with the blue dye technique and 79 only with lymphoscintigraphy. In the SLNs dissected during surgery the metastatic status was examined by sections at reduced intervals (at least 24 sections for each lymph node). Only patients with SLNs that were histologically positive for metastases underwent ALND.

We follow up our patients by monitoring the plasma levels of tumor markers (CEA, MCA, CA 15-3) and by clinical visits every six months. All patients undergo mammography once a year.

**Results**

From March 2000 to September 2001 we studied 201 patients with early stage breast cancer (mean age, \(\pm SD\) 61.5 \(\pm\) 10.4 years). We localized one or more SLNs in 194 (96.5%) patients. Lymphoscintigraphy alone detected one or more SLNs in 72/79 patients (91.1%); in patients with a positive scan an average of 1.2 SLNs were visualized. Blue dye alone detected SLNs in 25/25 patients (100%). With both techniques we identified one or more SLNs in 97/97 patients (100%).

Histologically, 40/194 patients (20.6%) showed SLN metastases (15/194, 7.8% micrometastases; 25/194, 12.9% metastases); 68% of these patients also had metastases in other axillary nodes. None of the patients with histologically negative SLNs developed metastases during follow-up (negative predictive value 100%).

**Discussion**

One of the most important advances in the surgical treatment of early stage breast cancer has been the introduction of SLN dissection as an alternative to routine ALND.\(^6\)\(^,\)\(^7\) This minimally invasive procedure may reduce the morbidity of surgical treatment and improve staging of the axillary lymph node basin.\(^8\)

Investigators at many cancer centers have verified that the SLN is the first lymph node to receive lymphatic drainage from a primary breast cancer and therefore the lymph node most likely to contain metastatic tumor cells.\(^1\)\(^-\)\(^14\) On the basis of this assumption histological assessment of the SLN increases the likelihood of detecting metastatic tumor cells; there is an overall 10% improvement in detection of nodal metastases with lymphatic mapping.\(^15\) The tumor status of the SLN should accurately predict the histopathological status of the regional lymphatic basin draining the tumor; in particular, a tumor-free SLN would exclude tumor spread to the regional lymphatic basin at risk.\(^9\) There is a 1-2% chance of positive nodes being missed, but in all series this omission appeared to result from a learning curve for the procedure.\(^10\)

The risk/benefit analysis of lymphatic mapping indicated an improvement in staging with reduced morbidity and elimination of the general anesthesia, surgical drain and hospital stay for nearly 80% of the patients in our series. With these concrete and significant advantages it seems apparent that lymphatic mapping will soon become the standard of care for early stage breast cancer. However, for a definite answer two prospective randomized trials using SLN biopsy have been undertaken in the United States.\(^11\)

**References**

SENTINEL LYMPH NODE BIOPSY TO STAGE PATIENTS WITH CUTANEOUS MELANOMA AT THE NATIONAL CANCER INSTITUTE OF NAPLES. RESULTS FROM 240 SENTINEL NODE BIOPSIES

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Abstract
Aims and background: The presence of lymph node metastases in patients with cutaneous melanoma represents the basis for correct therapy planning and is the most powerful prognostic factor to evaluate overall survival at diagnosis. Methods and study design: Since 1992, when Dr Morton published his first experience, the sentinel lymph node (SLN) biopsy technique seems to have solved this matter by correctly staging patients. We analyzed our data from 240 SLN biopsies performed in the last five years at the National Cancer Institute of Naples, evaluating the total identification rate and the nodal recurrence rate, and compared them with the preliminary data of the MSLT (melanoma sentinel lymph node trial). Results: Of all SLNs evaluated 18.5% were micrometastatic and 14% were identified by immunohistochemical staining. Forty-one patients had metastatic SLNs and nodal dissection of the positive basins revealed no other tumor-positive lymph nodes in more than 80% of them. All patients with a Breslow thickness of less than 2 mm had micrometastases only in the SLN, while with increasing thickness two, three or more positive nodes were found. Among SLN-negative patients nine (4%) developed lymph node recurrence in the previously treated basin and were therefore considered as false negative SLN biopsies. Conclusions: The prognostic value of SLN biopsy needs to be confirmed by the final results of the MSLT (melanoma sentinel lymph node trial). The prognostic value of SLN biopsy needs to be confirmed by the final results of the MSLT evaluating the therapeutic use of this procedure in patients with a Breslow thickness of less than 2 mm and its possible impact on the course of the disease.

Key words: cutaneous melanoma, lymphadenectomy, sentinel node biopsy.

Introduction
Lymph node status is the most important prognostic factor in melanoma. Sentinel lymph node (SLN) biopsy seems a good staging method but further data are needed to determine its impact on overall survival. The reliability is well established and we ought to analyze our experience in patients with cutaneous melanoma comparing results between positive and negative cases, with particular analysis of complications and nodal recurrences.

Materials and methods
In the period from June 1996 to June 2001 we performed 240 SLN biopsies in 221 patients. All patients had melanoma with a Breslow thickness of more than 1 mm or Clark IV-V. Primary lesions had been excised with a margin of less than 1 cm within three months of diagnosis. The patients were 119 females and 102 males with a mean age of 45.8 years (range, 16-87 years). To exclude nodal or distant metastases all patients underwent clinical evaluation, chest X-ray and liver ultrasound. Patients in whom a wide excision had been performed with a margin of more than 3 cm and those who had undergone a rotation flap procedure were excluded. According to Breslow’s classification 74 patients (33.5%) had a primary melanoma with a thickness between 1-2 mm, 53 (24%) between 2-3 mm and 77 (35%) of more than 3 mm; 84 primary lesions (41%) were ulcerated and in 17 cases information about primary lesion thickness was not available. The site of the primary lesion was the trunk in 110 patients (50%), lower extremities in 73 (33%), upper extremities in 26 (12%), and head and neck in 11 patients (5%). Lymphoscintigraphy was performed 2 to 4 hours before surgery following intra-dermal perilesional injection of human serum albumin labeled with 99mTc; coronal, sagittal and oblique images were obtained. The hot spot was marked on the skin. About 20 mins before surgery 1 mL of Patent Blue V was injected intradermally around the scar of the primary lesion and the skin mark was checked by an intraoperative probe to center the incision. In patients with more than three draining basins or without any drainage only wide excision was performed. The identification of blue and hot nodes was guided by the probe with correlation of radioactivity in vivo, ex vivo and in the operative field to ensure that all sentinel lymph nodes had been removed. Wide excision of the scar with a margin in proportion to the Breslow thickness was finally performed. Sentinel nodes were analyzed by H&E and immunohistochemical staining with HMB-45 and S-100. No frozen section was performed. Patients with micrometastatic nodes were submitted to lymphatic dissection of the positive basin; in case of negative H&E but positive immunohistochemical staining in lymph nodes in the groin only a superficial dissection was performed.

Results
Since in 19 patients lymphoscintigraphy revealed double drainage, a total of 240 SLN biopsies were performed. The SLN identification rate was 89% including the group of 40 patients at the beginning of our experience in whom SLN biopsy was performed without the use of the intraoperative probe. In 95% of groin dissections, 92% of axillary dissections and 84% of neck dissections the SLNs were correctly identified. In 13 cases the SLNs were localized in popliteal, suprascapular, occipital and epitrochlear basins with an identification rate of 85%. Nodal metastases were found in 18.5% of SLN biopsies and in 14% of them by means of immunohistochemical staining. The non-SLN identification rate was very low for inguinal basins and higher for axillary and cervical basins, correlating with the anatomical difficulties of these regions (Table 1). Forty-one patients had metastatic SLNs and nodal dissection of the positive basins revealed no other positive lymph nodes in more than 80% of cases. In this group all patients with a Breslow thickness of less than 2 mm had micrometastases only in the SLN, while with increasing thickness two, three or more positive nodes were found (Table 2).

Table 1 - SLN identification rate

<table>
<thead>
<tr>
<th>SLN biopsy (1996-2000)</th>
<th>240 dissections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axi (132)</td>
<td>92</td>
</tr>
<tr>
<td>Groin (89)</td>
<td>95</td>
</tr>
<tr>
<td>Cervic (6)</td>
<td>84</td>
</tr>
<tr>
<td>Other (13)</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
</tr>
</tbody>
</table>
No perioperative complications occurred and in only 14 (5.8%) of patients there was seroma formation in the treated basin, mostly in the inguinal area. Follow-up ranges from 108 to 6 months (mean, 33 months). Among the SLN-negative patients nine (4%) developed lymph node recurrences in the previously treated basin; these were considered false-negative SLN biopsies. Five (2.2%) patients had nodal recurrence in a basin not previously treated as the SLN site; four of them, all with primary melanomas of the trunk that were thicker than 2 mm, developed metastasis in the contralateral axilla. Among the patients with positive SLNs only one relapsed in the previously dissected basin, while three patients developed lymph node metastases in a different basin, two of them in the supraclavicular region after axillary dissection.

Discussion

The presence of lymph node metastases in patients with cutaneous melanoma represents the basis for correct therapy planning and is the most powerful prognostic factor to evaluate overall survival at diagnosis. Elective radical node dissection has been proved to have no impact on survival and has a high morbidity rate compared to therapeutic surgery. Since 1992, when Dr Morton published his first experience, the SLN biopsy technique seems to have resolved this matter by correctly staging patients. Many groups have evaluated the feasibility of this technique and it will be further validated by the MSLT (melanoma sentinel lymph node trial), whose accrual phase will be completed at the end of this year. Recently Morton published the preliminary results of this trial comparing the JWCI (John Wayne Cancer Institute) and MSLT experience, confirming the reproducibility of the procedure. The overall SLN identification rate is similar for JWCI and the centers participating the trial worldwide: 95.3% and 93.3%, respectively. Axillary dissection does less well compared to the other basins, probably due to the particular three-dimensional morphology of this area. Our data are similar with a 92%, 95% and 84% identification rate for axillary, groin and neck basins, respectively. The advent of the intraoperative probe has provided a more sensitive tool to identify SLNs, especially in the axillary region. Gershenwald reported 100% SLN identification by combining blue dye with the intraoperative probe. The incidence of SLN micrometastases was also similar in the studies: 22.6%, 18.7% and 18.5% for JWCI, MSLT and our data, respectively, which confirms that the procedure can correctly stage patients at the moment of diagnosis with a minimally invasive approach. Our false-negative rate, considered as the incidence of relapse in the basin previously treated with SLN biopsy, is about 4%; this is somewhat higher than the 2% of Gershenwald, probably because we included 40 early cases (between 1996 and 1997) where SLN biopsy was performed without the use of an intraoperative probe. Seventy percent of these relapses occurred in axillary basins, confirming the particular difficulty of SLN dissection in this area.

Many papers emphasize the role of SLN biopsy as a therapeutic procedure because patients with a Breslow thickness of less than 2 mm have micrometastases only in the SLN and all other lymph nodes removed with radical dissection are free of disease. In our experience the number of metastatic lymph nodes correlated with the Breslow thickness and patients with a melanoma thicker than 3 mm had more than two involved nodes in about 40% of cases, with a bad impact on prognosis. Further study will be necessary to verify if SLN biopsy can be considered as a therapeutic procedure in patients with a Breslow thickness of less than 2 mm.

Recently we investigated the role of RT-PCR assay on paraffin-embedded SLNs. Our analysis confirmed the support of the molecular assay to histopathological staining and a significant correlation with stage of disease and the risk of recurrence. The expression of mRNA markers in SLNs has a clinical predictive value in terms of disease-free survival and overall survival, but is not useful for predicting the metastatic stage of a negative SLN biopsy.

Cascinelli and Gershenwald reported a better survival for patients with nodal metastases compared with those who developed clinical adenopathies, but only the MSLT will definitively verify the prognostic value of sentinel biopsy and in which range of Breslow thickness it could change the outcome of the disease.

References


Table 2 - Number of positive nodes after dissection

<table>
<thead>
<tr>
<th>Lymph node status after dissection in PTS with POS SLN</th>
<th>1 N+</th>
<th>2 N+</th>
<th>&gt;3 N+</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mm (9 pts)</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-3 mm (11 pts)</td>
<td>91%</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>&gt;3 mm (21 pts)</td>
<td>67%</td>
<td>29%</td>
<td>4%</td>
</tr>
</tbody>
</table>
RELIABILITY AND ACCURACY OF SENTINEL NODE BIOPSY IN CUTANEOUS MALIGNANT MELANOMA

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Abstract

Aims and background: The aims of this study were 1) to investigate whether sentinel lymph node (SLN) biopsy could become the method of choice for the early detection of metastatic disease in patients with malignant melanoma and 2) to identify those patients with lymph node metastases who could benefit from regional lymphadenectomy. Methods and study design: Our study started in March 1998 and involved 110 patients with primary cutaneous malignant melanoma stage I or II (AJCC) in whom the primary lesion had been surgically removed no more than 90 days previously. On the day of lymph node dissection patients were given an intradermal injection of colloid particles of human serum albumin labeled with technetium-99m and an injection of isosulfan blue. The surgical procedure was usually performed with local anesthesia but in some cases locoregional or general anesthesia was preferred. Contralateral and ipsilateral lymphatic districts were scanned with a hand-held gamma camera (Scin- tin) before starting the surgical procedure. We injected intradermal a hand-held gamma camera to measure the background and identify the hotspot indicating the location of the sentinel node to direct the incision. Results: The combined use of lymphoscintigraphy, isosulfan blue and gamma probe allowed us to identify sentinel nodes in 90 cases (81.81%). The SLN was positive for metastases in 13 of the 108 patients (12.03%) and regional and distal lymphadenectomy was performed in all of them. The distribution of positive SLNs by primary lesion thickness was as follows: 0.76-1.5 mm: one positive SLN/44 patients (2.27%); >1.5 cm margin: two positive SLNs/51 patients (11.7%); >4 mm: six positive SLNs/15 patients (40%). Only four of 12 patients with ulcerated cutaneous melanoma had positive SLNs. The patients in our study underwent follow-up visits every four months. The median follow-up was 481 days (range, 97-1271 days). Conclusions: In patients with primary cutaneous melanoma the histological status of the SLN accurately reflects the presence or absence of metastatic disease in the relevant regional lymph node basin. Complete lymph node dissection should only be performed in patients with positive SLNs. Patients with lesions >4 mm are likely to develop recurrences and to die of systemic disease, so in these patients the usefulness of SLN biopsy is questionable. In conclusion, sentinel node mapping is a rational approach for the selection of patients who might benefit from early lymph node dissection of the affected basin.

Key words: malignant cutaneous melanoma, sentinel lymph node.

Introduction

The incidence of cutaneous melanoma continues to rise worldwide at a rate of about 5% per year1. Every day 12 women and seven men die of melanoma. Standard treatment includes adequate resection of the primary tumor, together with regional lymphadenectomy for clinically suspicious or pathologically positive lymph nodes2. Surgery remains the only effective option in the treatment of nodal metastases from cutaneous melanoma since chemotherapy and radiotherapy do not achieve the same cure rate in patients with nodal disease. However, the indications for performing elective lymph node dissection (ELND) or delayed lymph node dissection (DLND) are still being debated3.

In 1992 Morton and colleagues developed the hypothesis that the first lymph node (sentinel lymph node, SLN) draining the primary tumor is the first to develop metastatic disease. If this hypothesis is correct, excision of the SLN would allow the surgeon to correctly identify those patients with lymph node metastases who could benefit from regional lymphadenectomy and to avoid unnecessary procedures in patients without regional lymph node involvement4.

Material and methods

Our study lasted from March 1998 to October 2001 and involved 110 patients (63 males and 57 females with a median age of 56.5 years) with AJCC stage I or II primary malignant melanoma of the skin. All patients had histologically confirmed malignant melanoma which had been excised with a small surgical margin (<2 cm) no more than 90 days previously; tumor thickness was more than 0.75 mm. None of the patients had palpable lymph nodes at clinical examination. The location of the primary melanoma was the head and neck region in 10 patients, the upper limbs in 21, the trunk in 36, and the lower limbs in 43 patients.

On the day of lymph node dissection patients were given an intradermal injection of 0.2 mL (10-15 MBq) colloid particles of human serum albumin labeled with technetium-99m. The radiopharmaceutical was injected centrally at both sides of the scar of the diagnostic excision. 99mTc nanocolloid is transported through the lymphatic system and lodged in the SLN, which can be visualized by dynamic acquisition using a gamma camera. In our patients anterior and lateral static views were obtained 1-2 hours following injection of the radiopharmaceutical. The location of the SLN was marked on the skin with a cobalt-57 pen marker. Dynamic lymphoscintigraphy may sometimes visualize sentinel nodes in more lymphatic districts and in such cases biopsy at all these sites is necessary.

Before starting the surgical procedure we injected intradermally, at the same point of the colloid, 1-2 mL isosulfan blue and massaged the cutaneous area for 10-15 seconds to facilitate distribution of the dye through the lymphatics.

The surgical procedure was usually performed under local anesthesia but in some cases (depending on the site and number of SLNs, the site and characteristics of the primary lesion, and patient tolerance) locoregional or general anesthesia was preferred.

Contralateral and ipsilateral lymphatic areas were scanned using a hand-held gamma camera to measure the background and identify the hot point indicating the location of the sentinel node to direct surgical incision4. This was done after wide re-excision of the primary lesion to reduce background radiation to a minimum. Surgical treatment of primary melanoma includes wide (1 cm margin) re-excision of the primary lesion4. Excision is extended to the muscular fascia without including it, unless it is directly invaded.

At the point of the highest counts a small cutaneous incision (2-3 cm) was made to identify blue lymphatics and the SLN. Once the SLN was found and excised the lymphatic basin was checked for other SLNs and any remaining radioactivity.

Histopathological examination of the SLN was performed using Cochrane’s method5. The SLN was dissected into couples of serial sections of 3 microns at 100 micron intervals for a depth of 2 mm. Each section was stained with hematoxylin and eosin.
Immunohistochemical techniques have further improved the diagnostic sensitivity of detecting occult tumor cells in the regional lymph node basin. The most common targets of immunohistochemical staining for melanoma are the S-100 protein and HMB-45 antigen.

Results

The combined use of lymphoscintigraphy, isosulfan blue and gamma probe allowed us to identify the SLN in 108 of 110 patients (98.18%), while the SLN was blue in only 90 cases (81.8%). In two patients the SLN was not identified by either scintigraphy or gamma probe and isosulfan blue during surgery. Failure of SLN identification was probably due to interruption of the lymphatics by surgery and to sclerotic scar tissue.

In one patient with cutaneous malignant melanoma of the shoulder scintigraphy failed to show the SLN owing to drainage of the axilla in proximity to the injection site; the SLN was retrieved intraoperatively by gamma probe.

The SLN was positive for metastases in 13 (12.03%) of the 108 patients and regional and distal lymphadenectomy was performed in all of them. In six of the 13 patients who had subsequent lymph node dissection the SLN was the only positive node; micrometastases were present in five of these six patients and macrometastases in only one. In the remaining patients with more than one positive lymph nodes the SLN contained macrometastatic disease.

Lymphoscintigraphy in 108 patients showed drainage to different basins harboring 129 SLNs. Drainage to a single basin was seen in most patients (95; 87.96%), whereas drainage to two basins was seen in 13 patients (12.03%) with primary lesions of the trunk.

In seven patients lymphatic drainage to the side opposite to the primary melanoma was observed; one patient with melanoma located on the right side of the neck had drainage to a left cervical SLN and six melanomas located in the middle area of the trunk had unpredictable lymphatic drainage. The distribution of positive lymph nodes in relation to primary lesion thickness is presented in Table 1. Only four of 12 patients with ulcerated cutaneous melanoma had positive SLNs.

Patients underwent follow-up visits every four months including physical examination, ultrasonography of the liver and the spleen, chest x-ray. The median follow-up was 481 days (range, 97-1271 days). During follow-up four patients, all with primary lesions >4 mm, showed disease progression although SLN biopsy had revealed a pathologically negative SLN. In these cases radical therapeutic lymphadenectomy was required: three patients had local lymph node metastasis while one patient presented in-transit metastases as well as lymph node involvement.

Failure of SLN identification was probably due to interruption of the lymphatics by surgery and to sclerotic scar tissue. While learning the procedure, surgeons must complete lymph node dissection after biopsy of the sentinel node to monitor the presence or absence of metastatic disease in the relevant regional lymph node basins. If the SLN does not contain metastases, other nodes in the district concerned can be expected to be negative; this means that unnecessary procedures in patients without regional lymph node involvement can be avoided. Complete lymph node dissection should be reserved for patients with positive SLNs.

The sentinel node technique is based on the concept that regions of the skin have specific patterns of lymphatic drainage not only to the regional lymphatic basin but also to a specific lymph node in the basin. In cutaneous malignant melanoma some unusual drainage patterns have been observed and several unusual pathways identified. This calls into question the validity of the results of several studies of ELND that were not guided by pre-operative lymphoscintigraphy. ELND may be misdirected in up to 50% of cases without the aid of lymphoscintigraphy. In our own experience there was unusual lymphatic drainage in six (6.59%) patients; in five of these patients the melanoma was located 10 cm off the midline of the trunk and in one patient the primary tumor site was in the neck.

Lymphoscintigraphy is an extremely accurate method of identifying all nodal basins at risk for metastatic disease; the advantage of lymphoscintigraphy over classic anatomic indicators is the scan’s reflection of functional and not just structural anatomy.

It is well known that patients with lesions <1 mm almost always have local disease only, whereas patients with lesions >4 mm have an approximately 60% risk of regional metastases and a 70%-80% risk of distant metastases within three years. In our experience only four patients showed disease progression after a negative SLN biopsy and in all of them the thickness of the primary lesion was >4 mm. Patients with primary lesions >4 mm often develop recurrences and die of systemic disease despite an ELND that removed occult metastases. However, with the advent of effective adjuvant therapy SLN procedures should be offered to these patients for staging purposes. Patients with thick melanomas who also have documented nodal microscopic disease have a worse outcome than patients with thick melanomas and no signs of nodal spread. These patients (T4N1) were also in the subset of patients who benefited from adjuvant interferon alpha-2b. Our data confirm that SLN biopsy can be used in intermediate-thickness melanoma (1-4 mm) but also in melanoma >4 mm without palpable lymph nodes.

Sentinel node biopsy is a procedure requiring a multidisciplinary approach including surgery, nuclear medicine and pathology. A learning curve exists for the multidisciplinary team and caution should be exercised by using quality control measures and validating results. While learning the procedure, surgeons must complete lymph node dissection after biopsy of the sentinel node to monitor the rate of immediate false negatives. Similarly, the learning curve for pathological analysis needs to include routine immunohistochemical staining of both sentinel and non-sentinel nodes because histology alone misses up to 14% of occult micrometastases.

In conclusion, the sentinel node concept is a rational approach for the selection of patients who might benefit from early dissection of the affected lymph node basin. This new strategy is being applied in an increasing number of institutes and has been entered into controlled trials in order to determine its efficacy. If multicenter selective lymphadenectomy trials or similar trials do not show any effect on survival, then sentinel node biopsy has no therapeutic value and patients must be informed accordingly. This technique could become the method of choice for the early detection of metastatic disease.

Table 1 - Distribution of positive lymph nodes relative to primary lesion thickness

<table>
<thead>
<tr>
<th>Thickness (mm)</th>
<th>No. of patients</th>
<th>Positive SLN (%)</th>
</tr>
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<tbody>
<tr>
<td>0.76-1.5</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>1.51-4</td>
<td>51</td>
<td>6</td>
</tr>
<tr>
<td>&gt;4</td>
<td>15</td>
<td>6</td>
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References

RECENT APPLICATIONS OF THE SENTINEL LYMPH NODE CONCEPT: PRELIMINARY EXPERIENCE IN PROSTATE CANCER

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Abstract

Aims and background: Following the widespread use of radioguided surgery (RGS) in melanoma and breast cancer, we applied this new surgical strategy to prostate cancer (PC). The aims of this study were 1) to evaluate the accuracy of RGS in the detection of prostatic sentinel lymph nodes (SLN), and 2) to verify if pelvic lymphadenectomy (LAD) is an accurate means to detect solitary micrometastases. Study design: We investigated 48 patients with PC confirmed by transrectal biopsy who underwent radical prostatectomy and bilateral LAD. A dose of 99mTc-labeled nanocolloid particles was injected into the prostate after needle positioning by ultrasonography. Serial imaging was obtained with a gamma camera, identifying 1) the first radioactive lymph node (sentinel lymph node, SLN); 2) other radioactive lymph nodes, and 3) non-active lymph nodes. Results: Forty-three SLNs were identified in 48 patients. Twenty SLNs were located at unusual sites with respect to the extent of conventional LAD. Five SLNs were positive for micrometastases and two of these were located outside the usual LAD area. No micrometastases were found in any of the remaining lymph nodes (active and non-active). Conclusions: These preliminary results are in agreement with the few previous scientific contributions available on this topic and indicate that it is possible to reduce the extent and duration of surgery and necessary to reevaluate the conventional sites of lymphatic drainage.

Key words: lymphoscintigraphy, prostate cancer, sentinel lymph node.

Introduction

Following the widespread use of radioguided surgery in melanoma and breast cancer, we applied this surgical strategy to prostate cancer1-4. The aims of this study were to evaluate the accuracy of radioguided surgery in the detection of prostatic sentinel lymph nodes (SLN) and to verify if pelvic lymphadenectomy (LAD) is an accurate means to detect solitary micrometastases.

Materials and methods

Forty-eight patients (age range, 53-76 years) with biopsy-confirmed prostate cancer were included in this preliminary study. The PSA range was 2.7-51 ng/mL, the Gleason score range was 4-9, and tumor size ranged from 2 to 4 cm. All patients were informed about disease severity, diagnostic procedures and related therapeutic protocols.

Preoperative dynamic lymphoscintigraphy was performed to localize the SLNs. 99mTc-labeled colloidal albumin (nanocolloid) was injected directly under transrectal ultrasonic guidance. In 35 patients the tracer was injected two to three hours before surgery. The administered tracer volume was less than 1 mL, not exceeding a dose of 30 MBq. In 13 patients the tracer was injected in the same way and with the same volume the day before the operation, not exceeding a dose of 111 MBq. The tracer was injected at two different sites: into the tumor (by visual inspection) and into the contralateral lobe of the prostate (Figure 1).

Patients were positioned under a standard large-field-of-view gamma camera (matrix size 128 × 128), and lymphoscintigraphy was performed within 20-30 minutes of injection, until the first hot node (SLN) was clearly visible on the display. At this point acquisition was stopped. If the radiotracer did not flow along the lymphatic chain within 20-30 mins, imaging was repeated; in such cases delayed imaging was performed up to a maximum of three hours after injection.

Figure 1 - Tracer injected into the contralateral lobe of the prostate.
A hand-held gamma probe (ScintiProbe MR100 - Pol hi tech) was used for intraoperative localization of the SLN. The radioactive count rate of each node was registered before and after its excision. All detected lymph nodes were removed during subsequent radical prostatectomy.

During the learning phase of this study the surgeon always performed a complete lymphadenectomy after intraoperative scanning, regardless of lymphoscintigraphy findings, to monitor his rate of SLNs corresponding to false negative results. All specimens submitted to the pathologist were examined with standard staining and reading procedures.

Results

The SLN is usually the first hot node that appears within 20-30 minutes, but sometimes several lymph nodes are visualized at the same time. In these cases the hottest node is not always the SLN. Two nuclear medicine physicians blindly read LM (lymphatic mapping) and identified 43 SLNs out of 130 hot nodes. All these 43 SLNs were detected with the gamma probe during surgery and 20 were located outside the standard pelvic lymphadenectomy area. In eight patients we did not observe any radioactivity in the lymphatic chain up to 40 minutes. A peri prostatic hot node was observed in three of these patients with delayed imaging consisting of repeat acquisitions also at two and three hours after tracer injection. In the remaining five patients we failed to demonstrate SLNs both with early and delayed imaging.

The pathologist who examined all surgical specimens found micrometastases in five SLNs (Figure 2).

Two of these were located outside the range of standard pelvic lymphadenectomy, near the right hypogastric artery and at the left side of the bladder. No micrometastases were found in the other 87 non-SLNs.

Discussion

$^{99m}$Tc nanocolloid was the tracer of choice in our study. It is commonly available in nuclear medicine departments and good results have been reported in SLN detection by many investigators for various tumor types.\(^2\)\(^3\). After instant labeling at room temperature it is stable both in vitro and in vivo; nevertheless, administration to the patient was performed within a few minutes to ensure the best homogeneity in the dimension of the particles.\(^4\)\(^5\). The average administered volume was only 0.5-0.7 mL because larger volumes may alter the physiology of lymph drainage from the tumor, with unpredictable results.\(^6\)

Prostate tumors are usually multicentric and lymphatic drainage is widely variable. For these reasons the tracer was injected into the tumor but also into the contralateral lobe of the prostate. In only 30% of cases did the hypoechoic lesion closely correspond to the tumor.\(^7\) When the tracer was injected into the parenchyma surrounding the tumor the amount of radioactivity retained in the SLN was quite low.\(^8\) With a standard administered dose of $^{99m}$Tc nanocolloid the estimated dose to the surgeon is about 20 uSv/patient at a distance of 20 cm during an operation lasting one hour. Thus, radioprotection of operating room workers in SLN dissection is of minor concern.

Our experience seems to confirm that there are no significant differences in accuracy between single-day and separate-day approaches for SLN detection by lymphoscintigraphy. In both cases the registered activity with the gamma probe was significantly higher than the background activity. Focal uptakes of the tracer detected by lymphoscintigraphy were localized at the same sites by the gamma probe during surgery.

Only one SLN was not removed because it was located outside the surgical bed and too difficult to be isolated without increasing the surgical morbidity.

Conclusions

Our results are in agreement with those obtained by other investigators because this approach allows the excision of all SLNs found by lymphoscintigraphy. The technique represents a significant improvement in our ability to evaluate the status of regional lymph nodes. Moreover, the finding of SLNs outside the conventional pelvic lymphatic chain suggest that revision of standard lymphadenectomy is mandatory.

Only a larger number of lymphoscintigraphies will provide reliable information about the therapeutic relevance of this new approach. Close collaboration between surgeons, pathologists and nuclear medicine physicians is an essential condition to this goal.

References

PROGNOSTIC VALUE OF SENTINEL NODE IN ORAL CANCER

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Abstract

Aims and background: In stage I oral squamous cell carcinoma, clinical examination and imaging techniques are unable to identify 60-90% of patients at risk of micrometastasis, while the sentinel node biopsy technique allows to avoid the morbidity of elective neck dissection in patients not actually affected by micrometastases. Materials and methods: Forty-one T1-T2,N0 patients underwent lymphoscintigraphy after peritumoral injection of human albumin labeled with 99mTc. Focal areas of radiotracer uptake were marked on the skin preoperatively. The sentinel lymph node (SLN) was identified by the combined use of blue dye and gamma probe and subsequently removed. Complete neck dissection was then performed in all patients and the histological findings were compared with those of SLN biopsy. Results: The SLN was identified in 95% of the patients; in four cases (10%) two SLNs were isolated. In 18% of our patients the SLNs were located outside the expected drainage area. When the histology of the negative SLNs was compared with the pathological status of the neck dissection specimens no false negatives were found. Five SLNs in four patients contained micrometastases and were the only positive lymph nodes. Conclusion: SLN biopsy can be a valuable staging technique in T1 and T2 oral cancer with uninvolved neck in patients whose lymphatic drainage of the neck has not been altered by previous surgery or radiotherapy. It provides reliable detection of micrometastases, indicating which level(s) should be removed ipsilaterally or contralaterally, and allows the surgeon to accurately plan neck dissection, taking into consideration the pattern of lymphatic drainage of each individual patient. In this way unnecessary neck dissection and its morphofunctional sequelae can be avoided in a considerable number of patients.

Introduction

The presence of cervical metastases is the most important prognostic factor in patients with squamous cell carcinoma (SCC) of the oral cavity1-7. In fact, the five-year survival rate decreases by 50% in the case of single ipsilateral metastasis and by 75% when bilateral metastases are present; moreover, extranodal spread reduces the survival rate by a further 50%. The incidence of occult metastases ranges from 15% to 60%. The development of imaging techniques and sophisticated screening methods has made it possible to identify malignant lesions at an earlier stage; the lesions are therefore more often reduced in size and can be adequately treated before they spread to regional nodes2,3.

After histological evaluation of elective neck dissection specimens from patients with no palpable adenopathy, the false negative rate ranges from 12% to 41%; conversely, 35% of patients with a preoperative diagnosis of tumor-positive lymph nodes are found to be negative2. Imaging technology including ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) has improved the assessment of neck nodes but cannot identify micrometastases.

In this paper we report the results of 41 patients treated with sentinel lymph node (SLN) biopsy to assess the value of SLN detection in oral cancer. We used a lymphoscintigraphic technique and intraoperative detection by blue dye combined with a gamma-detecting probe to facilitate the identification and resection of the SLN.

Materials and methods

Our study included 41 consecutive patients with operable carcinoma of the oral tongue and floor of the mouth (cT1-T2) with negative lymph nodes on clinical and CT examination. Patients had not been previously treated with chemotherapy or radiotherapy and were scheduled to undergo modified type III neck dissection.

Two hours before surgery 5-7 MBq of 99mTc-labeled nanocolloids in 0.1-0.4 mL of saline was injected submucosally around the lesion. When the first lymph node draining the tumor was visualized by lymphoscintigraphy, it was marked on the overlying skin with India ink. Before the start of surgery, with the patient under general anesthesia, 0.5 cc of blue dye was injected in two equal doses of 0.25 cc on each side of the lesion submucosally. Ten minutes later a 2-3 cm incision was made in the neck at the point marked on the skin and the SLN was located, using the gamma probe and blue dye as guidance. After removal of the SLN the radioactivity in the operative field was checked to rule out the presence of any residual hot nodules. After SLN biopsy all patients received standard treatment for cT1-T2,N0,M0 squamous cell carcinoma of the oral cavity consisting of transoral tumor resection and comprehensive modified neck dissection (levels I-V).

Patients underwent follow-up visits consisting of clinical examination and US examination of the neck every three months for the first two years and every six months thereafter, in addition to yearly chest X-ray.

Several sections were obtained from each node at different levels and stained with hematoxylin and eosin.

Results

SLNs were identified by lymphoscintigraphy in 39 (95%) of the 41 patients and always within 15 minutes of tracer injection. In four cases (10%) two SLNs were seen: in two patients they were both ipsilateral to the tumor and in two cases they were bilateral. In seven cases (18%) SLNs were outside the expected drainage area and located at levels IV and V. All SLNs were removed and in the patients with bilateral SLNs bilateral modified neck dissection was performed.

Thirty-eight SLNs in 35 patients (two cases with bilateral SLNs and one with two ipsilateral SLNs) proved to be tumor-negative at final pathology and correctly predicted the pathological status of the neck dissection specimens. These patients are all disease free at the time of writing. Five SLNs in four patients (one case with two ipsilateral SLNs) contained micrometastases and were the only metastatic nodes identified.

Follow-up ranged from 12 to 61 months and only one patient developed contralateral metastases in the neck 10 months after surgery. The other patients are all disease free.

Discussion

Lymphoscintigraphy is currently a standard technique in the management of melanoma and breast cancer8 but its role in head and neck cancer is still debated9.

Our patients underwent a one-stage procedure including both primary surgery and neck dissection in order to avoid possible modifications of the lymphatic drainage, as reported by other authors10,11. Lymphoscintigraphy showed neck nodes with radiotracer uptake in all 41 patients investigated, and the combined intraoperative use of a hand-held probe and blue dye allowed suc-
cessful identification and removal of SLNs in 39 patients (95%). Koch et al. used a gamma probe to detect SLNs in five N0 patients with head and neck SCC (2 tongue, 1 mandibular gingiva, 1 tonsil, and 1 retromolar trigone) after injection of a radioluclide. In their experience SLNs were accurately identified in two cases and they concluded that SLN biopsy with a gamma probe is feasible, with potential saving of cost, time and morbidity, but requires testing in a larger patient cohort. Bilichik et al. in a similar study managed to find SLNs in five patients with head and neck SCC, but in this series, like in that of Koch et al., the cancer sites were too heterogeneous and neck dissections were not performed to evaluate the prognostic value of SLN for regional micrometastatic disease. In a recent paper by Alex et al. the authors accurately radiolocalized the SLN in all eight studied cases of head and neck SCC; there were no instances in which the sentinel node was negative for micrometastatic disease while non-sentinel nodes proved to be positive after complete neck dissection.

In our study, in all 39 cases in which SLNs were identified and removed, the pathologic status of the neck was always correctly predicted. In the four patients with metastatic SLNs, these were the only involved nodes, confirming the data of similar studies. In the group judged to have metastatic nodes, a percentage very similar to the data of the only involved nodes, confirming the data of similar studies. In the four patients with metastatic SLNs, these were removed, the pathological status of the neck was always correctly sentinet nodes proved to be positive after complete neck dissection.

Follow-up ranging from 12 to 61 months, with an average of 20 months, seems adequate to evaluate the reliability of SLN biopsy in oral cancer in the long term, revealing only one recurrence after surgery for SCC of the tongue. In our study lymphoscintigraphy showed separate lymphatic channels leading to distinct nodes at level IV or V. The seven cases (18%) with SLNs outside the usual lymphatic drainage area (level IV or V) correlated very closely with the data of Byers et al., who found that 15.8% of 277 patients had skip metastases as the only manifestation of disease in the neck after surgery for SCC of the tongue. In our study lymphoscintigraphy showed separate lymphatic channels leading to distinct nodes at level IV or V.

In conclusion, SLN biopsy can be a valuable staging technique in T1-T2 oral cancer with uninvolved neck in patients whose lymphatic drainage of the neck has not been altered by previous surgery or radiotherapy. It provides reliable detection of micrometastasis, indicating which level(s) should be removed ipsilaterally or contralaterally, and allows the surgeon to accurately plan neck dissection, taking into consideration the pattern of lymphatic drainage of each individual patient. In this way unnecessary neck dissection and its morphofunctional sequelae can be avoided in a considerable number of patients.

References


RADIOGUIDED OCCULT COLONIC LESION IDENTIFICATION (ROCLI) DURING OPEN AND LAPAROSCOPIC SURGERY

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Abstract

Aims and background: Intraoperative localization, during open and laparoscopic surgery, of small, nonpalpable colonic lesions located at peculiar sites or with concurrent inflammatory bowel alterations (diverticulosis, perivisceritis) is often difficult. The
aim of our work was to assess the validity of radioguided identification after preoperative labeling. Methods and study design: Patients who were candidates for colon surgery for occult lesions that, because of their size and location, were assumed to be difficult to detect, underwent colonoscopy I to 2.5 hours before surgery. A small dose of labeled albumin macroagregates was injected with a sclerotherapy needle into the subserosa underneath the lesion. Immediately following injection the lesion was identified with a transcutanously placed gamma detecting probe. Intraoperative tracer detection was performed either during open surgery or by means of a laparoscopic probe (detection time 3-5 mins). The position of the lesion was marked with a suture or with a clip. Surgery was performed according to the type of lesion to be treated. Results: In our initial clinical experience 15 colon lesions were preoperatively marked in 14 patients and were subsequently detected during surgery (four under laparoscopy) with a gamma detecting probe. This technique allows highly accurate, fast, and inexpensive surgical localization of lesions without irradiation and without complications. Conclusion: Our experience shows that preoperative endoscopic marking of nonpalpable colon lesions with 99mTc-labeled albumin macroaggregates followed by intraoperative detection with a gamma probe is a useful clinical method that is highly accurate and without complications.

Key words: colorectal tumors, laparoscopic surgery, radioguided surgery, surgical technique, tumor localization.

Introduction

The difficulty in colon surgery to detect certain lesions because of their small size or peculiar location is well known. Polyps, small neoplasms, tissue residues after incomplete endoscopic ablation and angiodyplasias are often difficult to detect both visually and by palpation. Lesions in the right and left flexure of the colon are also difficult to identify, especially when accompanied by inflammation (perivisceritis, diverticulosis). The problem is particularly evident in laparoscopic surgery, where lesion detection and lesion margin definition also for larger neoplasms with no serosa involvement are often quite complicated. The ideal method for accurate lesion identification should also be inexpensive and without complications. Several preoperative localization methods (eg double-contrast enema, colonoscopy) as well as marking and tattooing techniques (with India ink or methylene blue) have been proposed in the past to ensure accurate and effective surgery. However, intraoperative colonoscopy has long remained the most popular technique.

Recently, in an attempt to solve one of the major problems during laparoscopic colon surgery, namely proper lesion identification and lesion margin definition, a new technique was proposed consisting of preoperative endoscopic marking with clips followed by intraoperative detection by means of radiological equipment, metal detector or, more recently, ultrasonography.

Material and methods

Since September 1999 we have been using in our hospital an intraoperative radiotracer detector (ScintiProbe MR100, Pol hi tech, Aquila, Italy, with 18 LV-3 and 18 LVR probe and laparoscopic probe; cost: about 23,240 euro) during endocrine surgery (MIRP, minimvasive perothroidectomy), for sentinel lymph node detection in cancer surgery (breast cancer, melanoma), and for the detection of occult mammary lesions (ROLL). We have also employed this apparatus for occult colon lesion identification (ROCL).

Preoperative colonoscopy was performed 1-3 h before anesthesiathesis induction in 14 patients with colon disease. Under endoscopic guidance an amount of fluid corresponding to 1 cc of 99mTc-labeled MMA marker (1mCi = 37 MBq) was injected by means of a disposable varices injector (Wilson-Cook 23G). Injection was followed by transcutananeous checking with a gamma probe. In two of our patients the injection had to be repeated because of intraluminal radiotracer effusion. This was done with a regular follow-up, subsequent surgery and perfect labeled area detection. In spite of tracer effusion, no significant detection enhancement was observed in the colon portion downstream from the effusion area.

Transcutaneous detection with the 18 LV-3 probe ranged from 2300 to 4200 cps, whereas detection on the in vivo specimen amounted to 8500 cps, and on the isolated specimen to 10,000 cps. Endoscopy took 15-32 mins including colonoscopy, radiotracer injection and gamma probe detection of the localized signal as well as evacuation of air present in the colon. The syringe and the injection probe were disposed of as contaminated material. No special positions of the patient on the operating table are required for this technique. Only a tracer detection device is necessary with a manual intraoperative probe (covered with a standard videocamera cover or gas-sterilized) or a laparoscopic, gas-sterilized probe. The interval between injection and examination in the operating room ranged from 90 to 200 minutes.

The time necessary for lesion identification and clip marking ranged between three and six minutes when open surgery was performed, whereas during videoendoscopic surgery it took three to eight minutes to carry out these procedures. With an 18 LVR probe or a type 11 laparoscopic probe the background was assessed on the chest wall with the probe in cephalad position, together with the segment assumed to carry the lesion. The site was then marked with a clip. The lesion was resected and any uptake residue in the operative field and in the remaining abdominal cavity was checked. Lastly, the activity on the resected specimen was measured. A computer connected to the gamma probe was used for energy window control. The histological specimen was manipulated as a “biological risk” material until radiotracer decay.

Results

Since November 1999 14 patients with colon disease have been examined by means of the radioguided technique with the following findings: three polypl abscesses with medium-grade dysplasia, two bulky adenomatous polyplabscesses with medium-grade dysplasia, one case of endometriosis with intraperitoneal involvement, four polyplabscesses with tumor lesions but no peduncle involvement, three adenocarcinomabscesses (ADK) and two granulomatous neoplasms in the same patient (for a total of 15 lesions). The topographic distribution of the lesions was as follows: three in the ascending colon, two in the transverse colon, three in the left flexure of the colon, three in the descending colon, and four in the sigmoid colon. In four cases a bulky neoplastic lesion was present in another colon segment which required multiple surgery in the same patient. The following operations were performed: two right hemicolectomies, two anterior sigmoid resections, one left hemicolectomy, one segmentary resection of the left colon, and 12 colotomies with lesion resection. Six operations were performed endoscopically and in two cases were converted to open surgery. In all examined cases, lesion localization proved to be highly accurate, allowing prompt detection during surgery.

When the probe was moved 0.5 cm away from the injection site, detection would fall from over 10,000 to 8000 cps; at 2 cm from the injection site the detection rate was less than 4,000 cps; at 5 cm it dropped to around 1000 cps; at 10 cm to less than 1000 cps; and in areas further away from the injection site the detection rate was the same as for the background (<100 cps on average). In all cases the presence of the lesion was confirmed by histological examination.
Discussion

Any surgeon who, during colon surgery, has ever failed to see or palpate the lesion or identify it on the screen is perfectly aware of the stress and the organizational difficulties involved, the waste of time, and the risks he or she has run to complete the operation properly. Preoperative colonoscopy, whether or not associated with a double-contrast enema, does not always allow accurate assessment of the distance between the lesion and the anal verge because of colon distension and stretching during examination. Planning intraoperative endoscopy or, even worse, having to perform it in an emergency, with all the difficulties involved in proper surgery timing, positioning the patient, preparing the operative field, ensuring sterile conditions, detecting the lesion under combined endoscopy open approach, may sometimes be quite demanding and even unfeasible. To this should be added the costs of sterile material and antibiotic coverage and the hourly cost of the operating room and a team of gastroenterologists with portable equipment.

On the other hand, preoperative endoscopic tattooing with stains (eg China blue, indocyanine green, patent blue) has not proved to be a safe, repeatable, and reliable method in clinical practice. This is mainly due to the irrepeatability of the stains and to the irrepeatability of an exact submucosal injection. This is a poorly reliable method which is also likely to cause major complications, and it has a high failure rate due to the following factors: the risk of injecting the dye into the peritoneal cavity, the risk of chemical reactions triggered by the dye at the injection site, stain removal difficulty, instability of some stains, and the difficulty to detect them intraoperatively at certain sites (for example the left flexure of the colon).

Recently proposed marking techniques with clip and X-ray detection, metal detector or ultrasonography also have their shortcomings. Clips sometimes get displaced, radiology is often misleading and requires radioprotection, metal detectors, while not easily available especially for laparoscopic application, in order to be effective require in situ application of a large number of clips. Detection with ultrasonography also has certain drawbacks: apart from dislocation, which may always occur, upstream colon clamping is required, as well as rectal administration of a saline solution to guarantee optimal ultrasound performance. It would thus seem that ultrasonography can be effectively employed only at the rectum-sigmoid level. In addition, an ultrasonographic device is required with open and laparoscopic probes.

The main advantage of the radioguided technique tested by us is the extremely high accuracy of marked lesion localization, which is quickly done, does not require any additional maneuvers to those required by surgery, has a low cost and is repeatable.

Radioguided detection of occult colon lesions (ROCLI) allows accurate localization of nonpalpable lesions and limited resection (in cases where radical resection is not necessary for oncological reasons); it also makes it possible to combine a resection at one site with minimal amination surgery at another site (for example, right hemicolectomy + colotomic resection of a sessile polyp on the left). In addition, smaller accesses in open surgery are made possible by accurate transcutaneous localization followed by intraoperative localization.

For videolaparoscopic surgery, where a safe method for spatial lesion identification is fundamental, the techniques of vital importance. It allows quick and accurate lesion detection, thus enabling the surgeon to properly plan the resection margins, in compliance with the anatomic structures involved and with a radical oncological approach, without prolonging surgery and under full safety conditions.

In our opinion, colon lesions that may be difficult to identify due to their size, texture, or anatomic site can be accurately detected with this technique. Lesion detection is achieved without additional stress to the patient, in a cost-effective, repeatable fashion, and without the risk of complications. Furthermore, with this technique a difficulty which normally accompanies laparoscopic surgery can be overcome, namely the accurate identification of nonpalpable margins, a requirement which is often the cause of conversion to open surgery.

The cost of the tracer, which is usually employed in nuclear medicine for lung scintigraphy, amounts to 0.77 euro per injected dose; the needle for endoscopic injection costs approximately 36.00 euro, while the camera cover costs 4.15 euro. In our experience, the cost of the detection probe, which is not too expensive and entails no additional expenses for disposable parts, has not been prohibitive. As a matter of fact, we use the same probe for sentinel lymph node detection in melanoma and breast cancer and for the detection of occult breast lesions (ROLL), as well as in minimally invasive parathyroid surgery (MIRP).

Other possible applications for the detection of occult gastric lesions, identification and removal of neuroendocrine tumors, and for sentinel lymph node detection in colon cancer are currently being assessed. With such a wide range of applications the cost of the equipment is rapidly amortized.

With regard to radiation protection, on the basis of the number of radioguided procedures carried out by a surgeon per year we have estimated an actual dose of 0.3 mSv. The recommended dose ceiling according to the current Italian regulations (Decree No. 230/95) is 1 mSv a year for non-exposed operators.

In conclusion, our experience with ROCLI has shown that this technique allows accurate identification of occult colon lesions, with a 100% success rate, no complications, and no risk of ionizing radiation contamination.

References

ROLE OF LYMPHOSCINTIGRAPHY AND INTRAOPERATIVE GAMMA PROBE GUIDED SENTINEL NODE BIOPSY IN HEAD AND NECK MELANOMAS

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Introduction

The progress in the development of diagnostic techniques over the last 20 years has made it possible to identify tumors at an earlier stage. In particular, the technique of sentinel node (SLN) detection has reduced the need for more invasive procedures of tumor staging. The aim of this study was to identify the sentinel lymph node and its complex drainage in patients with melanoma of the head and neck region. We will try to demonstrate that this technique gives the surgeon a choice between elective and total lymph node dissection.

Material and methods

In this study 41 patients (27 males and 14 females) were evaluated. All patients had a diagnosis of melanoma of the head or neck without any clinical evidence of lymph node metastases. The primary melanoma was located on the scalp in seven patients (17%), on the face in 21 patients (51%), on the ear in eight (20%), and in the neck in five patients (12%) (Table 1). In five patients the melanoma was still present at the time of lymphoscintigraphy, while in 36 patients the primary lesion had been removed. The thickness of the lesions was measured in all patients. We used the procedure first described by Morton in 19926. Lymphoscintigraphy was performed one day before surgery to identify the lymphatic basins that could not be recognized solely on the basis of anatomic knowledge. The radiopharmaceutical consisted of albumin particles ranging in size from 5 to 80 nm, labeled with technetium (Nanocolloid)7,8. About 40 MBq of 99mTc Nanocol was injected subcutaneously in the peritumoral region if the tumor was still present or around the scar if the primary lesion had been removed. After tracer administration 15-minute dynamic acquisition followed by static acquisition for five minutes was carried out with a gamma camera (Picker Prism 1000 XP)9-12. A cobalt flood was used to obtain a better anatomic image. Finally, to facilitate the resection a reference mark was made with a cobalt13 marker. For more precise isolation of the SLN methylene blue was injected just before surgery. Intraoperative identification of the SLN was done with a crystal scintillator NaI(Tl) probe (Navigator, Gamma Guidance System, USA)13,14.

Results

It is very difficult to identify SLNs in melanomas of the head and neck as this area is rich in lymph nodes, so the drainage could be directed towards several lymph node stations. Lymphoscintigraphy showed lymphatic distribution to more than one basin in 24 of our patients. Two basins were identified in 11 patients (26%), three basins in six patients (15%) and four basins in seven patients (17%). In 16 patients only one basin was found and in one patient no basins could be identified (Table 2).

The SLN was found in 40 of the 41 patients (98%). Eighty-five percent of the identified lymphatic basins were biopsied. The location of the visualized nodes was 25 submandibular ipsilateral to the lesion (31%), 23 laterocervical (29%), 17 parotid (20%), 5 preauricular (6%), 4 postauricular (5%), 3 buccal (3%), 2 supraclavicular (2%), 1 maxillary (1%), 1 spinal (1%), 1 submandibular contralateral to the lesion (1%) and in one patient no basins were visualized (1%). Lymph node metastases were found in ten patients (24%); three patients had metastases in more than one basin (30%). All patients with a positive SLN biopsy underwent total lymph node dissection. In seven of these patients the primary lesion had a thickness of = 3 mm, in two patients primary lesion thickness was in the range of 0.1-1.99 mm, and in one patient it was 2-2.99 mm. No complications occurred during this study and no morbidity was observed during hospitalization.

At the time of the present evaluation it was documented that 35 patients (85%) were still alive, three were dead (7%), one patient had developed distant metastases and was lost to follow-up, and two patients were lost to follow-up after surgery was taken. Of the ten patients who underwent a lymphadenectomy, nine were still alive and six were free of disease. The other three developed distant metastases (liver, lungs, brain and kidney); one of them had abandoned treatment. Patients had a follow-up from 1 to 40 months (median 21 months). In this period 33 of the 35 patients (94%) survived; 31 (94%) were free of disease, one developed distant brain metastases and one had a local recurrence and

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Table 2 - Lymphoscintigraphic procedure

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<th>No. patients</th>
<th>No. visualized lymphatic basins</th>
<th>Distribution visualized lymphatic basins (%)</th>
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Discussion

In order to administer adequate therapy, the clinician should know the biological characteristics and the pathways of spread of the tumor. The detection of the SLN in melanoma of the head and neck is not easy, because the lymphatic network of this region is variable and unpredictable. Lymphatic mapping of the head and neck therefore remains a considerable problem in clinical practice. In our study we successfully depicted two, three or four basins of drainage in 25 patients. These data stress the need to perform lymphoscintigraphy with both early dynamic acquisition and delayed acquisition. This combined approach allows imaging of multiple drainage routes. In our series we had only one false negative result, probably caused by micrometastases that prevented the flow of the colloid, occluding both the lymphatic vessel and the related SLN. This could be the reason why the lymphatic flow was deviated towards another lymph node that was erroneously identified as the SLN.

In agreement with the published literature, we found a correlation between the thickness of primary melanoma lesions and metastatic involvement: 70% of the patients with a tumor-positive SLN had a primary melanoma with a thickness of ≥3 mm; moreover, the patient with the false negative SLN also had a lesion thickness of ≥3 mm. Thus, the incidence of lymph node metastases rises with increasing melanoma thickness. This paper demonstrates that, considering the large number of patients (63%) with multiple lymphatic basins and the large number of cases (30%) with more than one involved lymphatic basin, it is fundamental to check the drainage of all lymphatic basins. Dynamic image acquisition allows to identify only the first lymph node and its related lymphatic duct. Using also delayed acquisition, other possible basins of lymphatic drainage may be identified. This combined approach allows imaging of multiple drainage routes. In our series we had only one false negative result, probably caused by micrometastases that prevented the flow of the colloid, occluding both the lymphatic vessel and the related SLN. This could be the reason why the lymphatic flow was deviated towards another lymph node that was erroneously identified as the SLN.

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Liver metastases. The latter patient had a false negative SLN and a lesion thickness of ≥3 mm. The scintigraphic data were compared with those of methylene blue; in all cases scintigraphy revealed more SLNs than methylene blue.

References

TECHNETIUM-99m TETROFOSMIN IMAGING IN MALIGNANT LYMPHOMAS

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Abstract

Aim: To assess the utility of 99mTc tetrofosmin (TF) scintigraphy as a diagnostic modality in lymphomas. Methods: Seventeen patients (14 with Hodgkin's disease and three with non-Hodgkin's lymphomas; age range, 10-59 years) were investigated. Planar and SPECT images of the supradiaphragmatic region (including neck and chest) were obtained. All patients were untreated at the time of the first scintigraphy. Follow-up scans after therapy were acquired in six patients (in five twice), so a total of 28 scintigraphic studies were performed. Mediastinal, pulmonary, cervical, supraclavicular and axillary activity was evaluated and results were compared in a blinded fashion with those of CT. Results: TF imaging demonstrated pathological focal uptake at 38 sites (16 in the mediastinum, eight in the lungs, four in the axillae, eight in the supraclavicular region and two in the cervical region) in 16 of 17 untreated patients; CT identified 24 lesions (16 in the mediastinum, two in the lungs, two in the axillae, two in the supraclavicular and two in the cervical region) in 17 patients. Scintigraphy detected 22 of the 24 lesions demonstrated by CT and revealed 16 unknown tumor sites in 10 patients. The only negative pre-treatment scintigraphy result was found in a patient with axillary lymph node involvement. On the first post-treatment scintigram there was a reduction in the number of visualized pathological sites (seven vs 16) in five of the six patients examined. The second follow-up study demonstrated only two lesions in two of the five patients examined. Conclusions: Our preliminary results indicate that TF imaging is effective in detecting supradiaphragmatic lymphoma lesions in untreated patients and suggest that serial scintigraphic studies may be suitable for monitoring response to treatment. However, larger series are needed to better define the possible role of TF scintigraphy in the follow-up of the response to therapy.

Key words: lymphoma, scintigraphy, technetium-99m tetrofosmin.

Introduction

In patients with malignant lymphoma accurate disease assessment is essential because it provides the basis for different treatment options. In the past 25 years the prognosis of lymphoma patients has markedly improved: depending on stage, about 75-90% of patients with Hodgkin’s disease (HD) and 40-50% of patients with high- and intermediate-grade non-Hodgkin’s lymphoma (NHL) are potentially curable. Conventional imaging techniques like computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) provide detailed morphological information about lymphoma manifestations; however, these methods are based on anatomic criteria and the detection of tumor lesions remains uncertain in some cases, especially in the context of treatment monitoring. 99mTc tetrofosmin (TF) is a lipophilic cation complex that was originally proposed for myocardial perfusion scintigraphy but proved useful also as a tumor-seeking agent. Its diagnostic properties in malignant tumors are not based on anatomic conditions but rather on the metabolic activity of tumor tissue; these characteristics make the radiopharmaceutical potentially useful also for the assessment of lymphoma patients.

The aim of the current study was to evaluate the possible role of 99mTc TF scintigraphy as a diagnostic imaging modality in detecting supradiaphragmatic lymphoma lesions and in assessing response to therapy.

Material and methods

Seventeen patients (five females and 12 males; age range, 10-59 years) with histologically proven malignant lymphoma (14 with HD and three with NHL) were studied. All patients were untreated at the time of the first scintigraphy. Follow-up scans after therapy (chemotherapy and/or radiotherapy) were acquired in six patients (in five twice), so a total of 28 scintigraphic studies were performed. 99mTc TF scanning was added to the standard diagnostic workup for each patient, and appropriate informed consent was obtained in all cases.

A commercial TF preparation was used; labeling and quality control procedures were carried out according to the manufacturer’s instructions. The equipment consisted of a dual-headed gamma camera (Millennium, GE, Milwaukee, USA) with a parallel-hole, high-resolution collimator. 99mTc TF in doses based on body weight, 220 MBq (minimum) to 740 MBq (maximum), was given intravenously and scintigraphy was started within 15 minutes of injection. Planar (anterior and posterior, 128×128 matrix, 10 min/each) and SPECT images (360°, 64×64 matrix, 64 projections of 30 sec/each) of the supradiaphragmatic region (including neck and chest) were acquired.

Scintigraphies were divided into five regions (mediastinum, lungs, left and right cervical, left and right axilla, left and right supraclavicular) and the detected abnormal foci of uptake were compared with CT findings. All images were blindly evaluated by two experienced nuclear medicine physicians who did not know patients’ clinical data, and classified as positive or negative for abnormal 99mTc TF accumulation; differences of opinion were resolved by consensus, with a third observer acting as a referee.

Results

On pre-treatment scintigrams 99mTc TF imaging showed abnormal tracer uptake at 42 sites in 16 of 17 patients, whereas CT identified 24 pathologic regions in 17 of 17 patients. The region most often affected was the mediastinum (Table 1). 99mTc TF scintigraphy identified 22 of the 24 lesions demonstrated by CT and revealed 16 additional unknown lesions in 10 patients. The only two lesions recognized by CT but not seen on scintigraphy were located in the axilla of one patient.

In the first follow-up scintigraphy after therapy, response to treatment was demonstrated by the disappearance of localized abnormal 99mTc TF accumulation in five of six investigated patients: only seven of the 17 previously identified lesions were still visible on scans. In the five patients who had two follow-up scintigraphies, focal 99mTc TF uptake had disappeared in the third study in three cases (four lesions in comparison with the first follow-up scan) and only two lesions in two patients were detected. There was good agreement between post-treatment 99mTc TF imaging results, response to treatment, and clinical outcome.
Discussion

In lymphoma CT and MRI are the reference imaging procedures both for primary diagnosis and follow-up; however, these methods cannot establish whether a lymph node of abnormal size has been invaded, nor can they exclude the possibility that a node of increased size is simply an inflammatory lesion. The prognosis of patients after therapy depends mainly on their response to treatment, but often neither CT nor MRI can differentiate between tumor relapse and fibrosis.

The shortcomings of conventional imaging methods have led clinicians to evaluate the possible role of functional images in the evaluation of lymphoma patients. A wide range of radiouclide agents, particularly those with high energy photons, have been employed to this end in the past; in particular, Ga-67 has been extensively used with good results in the management of lymphoma patients. However, FDG-PET has been found to be more sensitive than Ga-67 scintigraphy in the staging of lymphoma but is often not available, whereas TI-201 has significantly greater tumor avidity in patients with low-grade lymphoma compared with Ga-67, but its low photon energy does not make it an optimal imaging agent for tumor detection.

The tumor-seeking properties of $^{99m}$Tc TF are well known for various types of cancer: in tumor cell lines its accumulation depends on cell membrane and mitochondrial potentials and the low uptake observed in dead cells indicates that $^{99m}$Tc TF accumulation occurs only in viable tumor tissue. In the present study we have demonstrated that $^{99m}$Tc TF is useful in lymphoma: it was successful in recognizing supradiaphragmatic lymphomatous lesions. The biliary-intestinal route of elimination of the radiopharmaceutical makes investigation of the infradiaphragmatic region difficult; when this is required, dynamic study of the abdomen immediately following injection of the radiopharmaceutical may be helpful.

Response to treatment was demonstrated by the disappearance of focal uptake in previously pathological regions; this finding is important for the short-term management of therapy, in assessing the responsiveness of lymphomatous tissue and to verify the effectiveness of treatment. Our results indicate that serial $^{99m}$Tc TF PET has been able to more sensitively than Ga-67 scintigraphy in the staging of lymphoma but is often not available, whereas TI-201 has significantly greater tumor avidity in patients with low-grade lymphoma compared with Ga-67, but its low photon energy does not make it an optimal imaging agent for tumor detection.

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Response to treatment was demonstrated by the disappearance of focal uptake in previously pathological regions; this finding is important for the short-term management of therapy, in assessing the responsiveness of lymphomatous tissue and to verify the effectiveness of treatment. Our results indicate that serial $^{99m}$Tc TF PET studies may be suitable for monitoring response to therapy; however, larger series are needed to better define the role of $^{99m}$Tc TF imaging in the follow-up of lymphoma patients. Moreover, it would be interesting to investigate the relationship between TF accumulation in lymphomas and response to chemotherapy. In fact, the observation that $^{99m}$Tc TF uptake in breast cells in vitro is related to the P-glycoprotein encoded by the multidrug resistance gene suggests the potential usefulness of this radiopharmaceutical in evaluating in vivo the presence of multidrug resistance in tumors and in predicting treatment outcome also in lymphomas.

References


BREAST CANCER TAKES UP $^{99m}$Tc BOMBESIN: A PRELIMINARY REPORT

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Abstract

Background: Several tumors including lung, prostate, ovarian, colon, and exocrine pancreatic cancer show receptors for the amphiphilic neurotransmitter and growth factor bombesin (BN) and its mammalian counterparts gastrin-releasing peptide and neu-romedin B. Also breast cancer has been reported to show such receptors: the presence of BN receptors in primary breast cancer has been demonstrated on cultured cells and by autoradiography on breast tissue samples. Authors who have studied BN receptors in breast cancer do not agree on their frequency in primary can-cer, but indicate that 100% of metastatic breast cancers show such receptors. Methods: We examined three primary breast cancer patients with $^{99m}$Tc BN and $^{99m}$Tc sestamibi one week before surgery. One of them showed axillary node invasion. The same acquisition technique was used for breast and chest imaging with both radiopharmaceuticals, whereas total body images were acquired only with $^{99m}$Tc BN. Also the administered radioactivity was different: 20 mCi of $^{99m}$Tc sestamibi and 5-8 mCi of $^{99m}$Tc BN. Dynamic images were acquired for 20 mins after iv injection with the patient in ventral decubitus and the gamma camera positioned in lateral view, as is generally done in Kakhkhal's prone scintimammography. Anterior chest images were acquired for 30 mins. Prone scintimammography was performed one hour after administration of both tracers. ROIs were drawn on tumors and surrounding breast with the same technique in order to calculate the tumor to breast ratio (T/B). In addition, total body scan was performed one hour and three hours after $^{99m}$Tc BN administration. All three patients underwent breast conserving surgery with lymphadenectomy. Postoperative pathologic assessment showed the following T and N stages in the three patients: T3N1, T3N1, and T4N1. Results: All three cancers were imaged with both tracers. The T/B of $^{99m}$Tc BN was always higher than that of $^{99m}$Tc sestamibi. Chest uptake was always much higher with $^{99m}$Tc sestamibi. Chest uptake was always much higher with $^{99m}$Tc sestamibi. Chest uptake was always much higher with $^{99m}$Tc sestamibi.
BN is not taken up by vessels and inflammatory tissue. The time activity curves of the two tracers were significantly different in all patients, with an increase in $^{99m}$Tc BN uptake in the first three to five minutes, followed by a less sharp uprise of the curve, quite similar to a plateau. 

**Conclusions:** Our first impression is that $^{99m}$Tc BN is a useful breast cancer seeking agent and very promising for lymph node staging.

**Key words:** breast cancer, bombesin, lymph nodes, scintigraphy, technetium.

**Introduction**

Bombesin (BN) and mammalian BN-like peptides are small neuropeptides that act as neurotransmitters, releasing factors, morphogens and growth factors. BN receptors (BNR) are present in most tissues and overexpressed by some tumors, including prostate and colon cancer, gastroenteropancreatic endocrine tumors, and small cell lung carcinoma. The list of cancers overexpressing BNR is long and still growing. 

Overexpression of BNR by tumors is often associated with autocrine production of BN and epithelial growth factor receptor or other tyrosine-kinase receptor transactivation, this means that the hormone is a relevant factor in tumor growth and invasion. Although four BNRs have been identified, three receptors are generally present in normal and pathologic human tissues. Two of them are specific for gastrin releasing peptide (GRP) and neuromedin B, which are considered to be the mammalian counterparts of BN, while BN is basically a class of amphibian peptides; for the third receptor (BNR3) no specific mammalian peptide has been discovered, so BNR3 is also referred to as orphan. All three receptors can be overexpressed in human cancers, although not necessarily all in the same cancer. Amphibian BNs are able to bind to all three BNRs, albeit with different affinities. 

Overexpression of BNR receptors also occurs in breast cancer. Gugger and Reubi have recently shown that 62% of primary carcinomas and 100% of breast cancer metastases including lymph node metastases overexpress the gastrin-releasing factor subtype BNR. Gugger and Reubi’s pathologic observations have to some extent been confirmed by early data from human studies with $^{99m}$Tc-labeled GRP.

We have developed a synthetic BN-like pentadecapeptide that shows the same C-terminal amino acid sequence as amphibian leu13 BN. At the N-terminal end we replaced Phe by Cys, while providing a useful-for-technetium labeled space arm between the two N-terminal amino acids Cys and Gln. This space arm was a molecule of amino hexadecanoic acid. After having performed preclinical and initial clinical studies on humans, we started studying the uptake of $^{99m}$Tc BN in breast cancer using a single-step procedure. We administered 370-555 MBq, corresponding to 0.5-0.75 mg of BN-like peptide, to each patient after having checked the absence of free technetium with thin layer chromatography on a silica gel strip, with methanol 75% as solvent. With this method the RI of $^{99m}$Tc BN is 0.8 and the RI of free technetium is 1, whereas colloidal $^{99m}$Tc does not move.

$^{99m}$Tc BN scintigraphy

Dynamic acquisition was performed with the patient in the prone position with a double-headed gamma camera equipped with a parallel-hole, general-purpose collimator at a rate of 1 frame/min for 20 mins after iv injection of 10 to 15 mCi of $^{99m}$Tc BN. Static and whole body scans were then performed at 30 minutes, one hour and three hours.

$^{99m}$Tc sestamibi scan

Three to five days after $^{99m}$Tc BN scintigraphy, sestamibi scan was performed with the same technique, with the exception of whole body scans. ROIs were drawn on tumors, peritumoral tissue, breast background, chest and axilla. Time/activity curves were generated from the dynamic study and the tumor/breast ratio was calculated on dynamic and static images. The same procedures were applied to BN and sestamibi scans.

**Image interpretation**

Images, as well as whole data, were sent by e-mail from Tomsk to Rome and vice versa. Patients were identified by internal codes instead of names. Nuclear physicians with a broad experience in scintimammography who were unaware of the results of mammography, surgery and histology reviewed the scintigraphic images and curves. Scans were considered positive for breast cancer when there was a clear, well-defined hot spot within the breast image.

**Statistics**

Data are presented as average ± standard deviation. The sensitivity and specificity were not calculated because of the small number of patients.

**Results**

One tumor was located in the upper outer quadrant and the other two were deeply central, near the chest wall. The mammographic size was 0.8, 0.7 and 1.3 cm, respectively.

**Pathology**

All three lesions were infiltrating ductal carcinomas. Pathologic tumor staging was two T1b and one T1c; lymph node staging was two N0 and one N1.

**Sestamibi scan**

$^{99m}$Tc sestamibi prone scintigraphy was positive in the patient with T1c cancer and in one of the two patients with T1b cancer. In the two patients with a positive sestamibi scan the earliest appearance of the tumor was at two minutes after iv sestamibi administration.

**Bombesin scan**

The labeling yield was more than 89%; radiopharmaceutical quality control showed stability of the labeled molecule exceeding eight hours. No acute or delayed adverse reactions occurred in any of the patients. Whole body scans at 30 minutes and three hours showed uptake by tumors, liver and kidneys. The gut was visible three hours after tracer administration. The stomach was never imaged. A thyroid image was always present, but the gland appeared less intense.

**Material and methods**

Three patients with highly suspicious breast cancer aged 48, 63 and 67 years were studied with $^{99m}$Tc sestamibi and $^{99m}$Tc BN. They underwent surgery within two weeks of scintigraphy. Patients gave their written informed consent in accordance with the directions of the local ethical committee. One tumor was located in the upper external quadrant and the other two were deeply central, near the chest wall. The mammographic size was 0.8, 0.7 and 1.3 cm, respectively.

$^{99m}$Tc BN preparation

The radiopharmaceutical was prepared by the Demokritos Institute as a sterile, pyrogen-free kit containing 0.1 mg of lyophilized pentadecapeptide with the following amino acid sequence: Cys-Aca-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH$_2$, and of Sn Cl$_2$ in nitrogen atmosphere. The lyophilized kit was labeled with 740 MBq of $^{99m}$Tc pertechnetate using a single-step procedure. We administered 370-555 MBq, corresponding to 0.5-0.75 mg of BN-like peptide, to each patient after having checked the absence of free technetium with thin layer chromatography on a silica gel strip, with methanol 75% as solvent. With this method the RI of $^{99m}$Tc BN is 0.8 and the RI of free technetium is 1, whereas colloidal $^{99m}$Tc does not move.
active than on sestamibi scan. In one patient 99mTc BN scintigraphy detected only one lobe, whereas 99mTc sestamibi was taken up by both lobes. Thyroid as well as pituitary hormones were normal, as were thyroglobulin and antithyroid antibodies.

Technetium BN detected breast cancer in all three patients studied. Noteworthy, in all patients the tumor was clearly shown on prone scintimmammography from the first minute, i.e., the first frame of dynamic acquisition after iv tracer administration already showed the presence of cancer. In the patient with lymph node invasion, axillary nodes were imaged. The time activity curves showed fast uptake of the labeled peptide by the tumor and slower uptake by breast tissue. The tumor/chest ratio showed a fast increase in tumor activity from one to four minutes, followed by less rapidly increasing activity. T/B curves showed a fast increase up to four to five minutes, a plateau of six to eight minutes, and a slowly decreasing slope from 10 to 20 minutes.

**Comparison between 99mTc BN and 99mTc sestamibi scintigrams**

In general BN scan showed more radioactivity in cancer and less in normal breast tissue and chest than sestamibi. Moreover, the two cancers that were visualized with both radiopharmaceuticals appeared larger on BN than on sestamibi images.

Comparison between node imaging on BN and sestamibi scans was intriguing. Uptake of the invaded node gave a clear scintigraphic image with both radiopharmaceuticals. However, the image of the node as shown by BN was smaller and less active than the sestamibi image of the same node: just the opposite of what happened with images of the primary tumors.

Tumor/breast background ratio (T/B) was measured on the same ROIs at five minutes and one hour as shown in Table 1. Max T/B on sestamibi scan was measured in T1c cancer at five minutes as 1.62 and with BN – also at five minutes and in the same patient – as 1.9. The cancer/breast background ratio of BN scan was higher with BN than with sestamibi even at one hour, when T/B was 1.8 and 1.43 instead of 1.57 and 1.38, respectively, in the two tumors imaged with sestamibi. In the tumor that was not imaged with sestamibi a maximum T/B ratio of 1.41 was observed at five minutes.

### Discussion

Our pilot study shows that labeled BN is well labeled, stable and safe. Although these features had already been observed in preclinical studies, confirmation by the present study in humans was obviously important. 99mTc BN is taken up by breast cancer and by invaded lymph nodes. Bombesin was able to image tumors as early as one minute after iv injection with increasing uptake in the first minutes following injection. Also the breast uptake increased during the first 30 minutes following injection, and the tumor/breast ratio slightly decreased after a peak at 8-12 minutes. The slight decrease in the tumor/breast background ratio after 10-12 minutes probably does not reflect the washout of the radiopharmaceutical but just an increase in breast uptake. However, our very limited series of three patients only allows presuppositions and precludes any definite statements.

Significant differences between the BN and sestamibi T/B ratio occurred in all patients. This can be partly explained by the different uptake mechanisms of the tracers and partly by a less intense uptake in the chest of the hormone compared with sestamibi. As a consequence also background due to scattered radiation is less important on BN than on sestamibi images.

Auxiliary nodes were detected by both radiopharmaceuticals in the patient whose final pathological stage was N+. Node positivity was more intense on sestamibi than on BN scintimmammography, giving particular images on which the primary tumor was more evident with BN and the nodes with sestamibi. Immunohistochemical analysis demonstrated that BN was taken up only by metastatic cancer cells, while the lymph vessels, lymphocytes and inflammatory cells did not show any uptake; by contrast, the sestamibi image might be enhanced by aspecific uptake.

In conclusion, we have studied the accuracy of BN scintimmammography in the diagnosis of breast cancer by itself or in comparison with sestamibi was not among the aims of our pilot study; BN as well as octreotide and steroid hormone receptors are subject to a complex regulation, and it is therefore difficult to draw any conclusions in this respect. Moreover, the role of BN receptor overexpression has not been as extensively studied in breast cancer as in prostate or small cell lung cancer. For example, it has been reported that more than 30% of breast cancers do not show GRP receptors. Since we used scintigraphy with 99mTc [leu 13] BN rather than scintigraphy with 99mTc GRP or autoradiography with 125I [Ty r4] GRP, as Gugger and Reubi did, our data are not comparable with those of any previous study.

Our initial results encourage us to proceed with our study of the uptake of 99mTc BN in breast cancer. Although a pilot study cannot give any reliable information on the future use of a new radiopharmaceutical, we think that the attention will have to be focused on the possible use of 99mTc BN as a radioisotope to direct biopsies towards the most aggressive parts of a tumor. We have already guided breast biopsies with 99mTc sestamibi (Soluri A, Falcini F, Sala R, Scafè R, Burgio N, Fiorintini G, Giorgetti G, Stella S, Chiariini S, Scopinaro F: Mammotome breast cancer biopsy: combined guidance with X-ray stereotaxis and imaging probe. Functional breast imaging with advanced detectors. ISS, Rome, 18-21 April 2001. http://www.g3.iss.infn.it/~congresso/iss/index.htm. Accepted for publication in Nuclear Instruments & Methods, 2002. See also Scopinaro F: Role and perspectives of scintimmammography functional breast imaging with advanced detectors. ISS, Rome, 18-21 April 2001. http://www.g3.iss.infn.it/~congresso/iss/index.htm. Accepted for publication in Nuclear Instruments & Methods, 2002). A higher T/B ratio and heterogeneous distribution of BN within a tumor could improve our technique.

The second highly interesting feature of 99mTc BN could be its specific uptake by metastatic lymph nodes. If the present findings will be confirmed, it will be worthwhile to study BN uptake by lymph nodes in the context of breast cancer staging.

In conclusion, we have studied a new, well-labeled, safe and specific radiopharmaceutical that is taken up by breast cancer and its metastases with promising early results. Although it is not possible to predict its diagnostic accuracy, further studies on its use in primary breast cancer and in the diagnosis of lymph node invasion are warranted.

### References


Abstract

Aims and background: Bombesin-like neuropeptides work as neurotransmitters and growth factors at the same time. Several human cancers show overexpression of three receptors for mammalian counterparts of amphibian bombesins (ABNs), i.e. gastrin releasing peptide (GRP), neuromedin B (NMB) and possibly another peptide. ABNs in turn are able to bind to mammalian and human receptors in vitro, and it is therefore interesting to study radioisotope-labeled bombesin (BN) and BN-like peptides as cancer seeking agents. Methods and study design: Starting from the amino acid sequence of Leu1 ABN, the Demokritos Institute has synthesized and labeled with technetium a new BN-like peptide that has the same biological characteristics as the amphibian bombesin peptide; changes were made only in the N-terminal part of this tetradecapeptide. After having obtained satisfactory results with 99mTc BN in a preclinical study, we started a phase I trial involving cancer patients as well as normal volunteers in Tomsk.

Three normal volunteers, one patient with small cell lung cancer and one patient with primary prostate cancer were studied after iv injection of 185 MBq, corresponding to 0.7 micrograms of 99mTc BN. Dynamic images of the tumors were acquired for 20 mins, followed by SPET. Total body images were acquired in patients and normal volunteers 1 and 3 h after 99mTc BN acquisition. In patients involving cancer patients as well as normal volunteers in Tomsk.

Conclusions: 99mTc BN in a preclinical study, we started a phase I trial involving cancer patients as well as normal volunteers in Tomsk. Three normal volunteers, one patient with small cell lung cancer and one patient with primary prostate cancer were studied after iv injection of 185 MBq, corresponding to 0.7 micrograms of 99mTc BN. Dynamic images of the tumors were acquired for 20 mins, followed by SPET. Total body images were acquired in patients and normal volunteers 1 and 3 h after 99mTc BN acquisition. In addition, 99mTc sestamibi scintigraphy was performed in the patient with small cell lung carcinoma. Results: No relevant side effects were observed. Both tumors were well visualized on early 1-2 mins images with planar as well as tomographic imaging. Total body images showed radioactivity in the liver, kidneys and thyroid gland. The stomach and spleen were never imaged. Radioactivity was found in the urinary bladder 4 mins after injection in the patient with prostate cancer. Three-hour total body scans showed radioactivity in the duodenum. In the patient in whom also 99mTc sestamibi scintigraphy was performed, thyroid uptake was much higher with sestamibi than with 99mTc BN, whereas the uptake of small cell lung carcinoma was higher with 99mTc BN than with sestamibi. Conclusions: 99mTc BN is able to clearly image tumors with BN receptor overexpression. Our first impression is that in the future this radiopharmaceutical may serve as a cancer seeking agent and, due to its high tumoral uptake, also as a radiotracer for radioisotope-guided surgery.

Key words: prostate cancer, small cell lung carcinoma, 99mTc [Leu1] bombesin, 99mTc sestamibi.

Introduction

Bombesin (BN)-like peptides, like gastrin releasing peptide (GRP) and neuromedin B (NMB), which are the mammalian counterparts of BN, are involved as neurotransmitters in a wide
and complex variety of regulatory functions. BN receptors are present in central nervous system structures such as the amygdala, hypothalamus, and olfactory brain, where they regulate hunger-satiety and sleep-wake rhythms, and release of pituitary hormones. BN-like peptides show several other functions, eg release of gastrointestinal hormones and stimulation of intestinal and esophageal smooth muscle contraction. These hormones not only regulate the behavior of complex systems, they are also growth factors for normal tissues as well as for a variety of tumors showing overexpression of BN receptors, including small cell lung carcinoma, cancer of the prostate, colon, esocrine pancreas, and ovary, to mention just a few. Moreover, BN stimulation is particularly important because it is generally established by an autocrine loop.

In view of the presence of receptors on several tumors, various investigators have labeled BN-like peptides with radioisotopes in order to develop cancer seeking agents. We have synthesized the amphibian tetradecapeptide [Leu] BN, making two changes on the N terminus: the Pyr terminal was replaced with Cys and the two N terminal amino acids were spaced with aminohexadecanoic acid (ACA), in order to allow direct 99mTc labeling of this molecule.

After having successfully performed preclinical studies on rodents, in the present work we aimed to study our 99mTc BN as a cancer seeking agent in humans. An international research group worked in Tomsk (Russia), where this study was carried out.

Material and methods

Subjects

Two normal volunteers, one patient with prostate cancer and one patient with small cell lung carcinoma (SCLC) were included in the study. Informed consent was obtained from all participants according to the rules of the Tomsk oncology center. Prostate cancer was diagnosed with serum PSA assay and transrectal ultrasonography. Bone scan and whole body CT were performed to exclude metastases. Small cell lung carcinoma was diagnosed with chest X-ray, CT, and NSE assay. The healthy volunteers were physicians of the research staff who were regularly checked by physical examination and laboratory tests.

99mTc BN preparation

[Leu] BN with the aforementioned changes on the N terminus was prepared at the Demokritos Institute (Athens, Greece) as a sterile, pyrogen-free kit containing 0.2 mg of lyophilized peptide with the following amino acid sequence: Cys-Aca-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH2 (35,36) and of Sn Cl2 in a nitrogen atmosphere. The lyophilized kit was imaged with 99mTc BN. Duodenal and jejunal activity appeared at 1 h after injection as a hot spot caudal to the bladder and posterior to the urethra. In the normal male volunteer without known prostate disease and normal serum findings no such findings, which are suggestive of prostate cancer, were visible on planar dynamic images or SPECT.

SCLC was well imaged with 99mTc BN and 99mTc sestamibi. 99mTc BN detected three uptake zones on planar scan and four on SPECT, whereas the hot areas with sestamibi were two on planar and three on SPECT images. As with prostate cancer, also small cell lung carcinoma was well imaged by 99mTc BN 1-2 mins after injection, with increasing uptake for 5 mins. From 5 to 20 mins tumor radioactivity plateaued. At 1 and 3 h scintigrams visualized SCLC just as well as in the first 20 mins. Radioactivity ratios among the four zones of 99mTc BN uptake changed between 2-min and 20-min images and between 1-h and 3-h images due to an increase in radioactivity in the two small tumor nodules compared to the two larger nodules that were detected also by sestamibi scan.

Total body scans showed major radioactivity uptake by tumors, liver and kidneys. The thyroid gland was faintly imaged: in the patient studied with 99mTc BN and 99mTc sestamibi the thyroid-to-neck activity ratio was much higher on the 99mTc sestamibi scan than on the 99mTc BN scan. The stomach was never imaged with 99mTc BN. Duodenal and jejunal activity appeared at 3 h on 99mTc BN total body scintigrams in all patients but one. The bladder was visible at 1 as well as at 5 h.

Discussion

Our data indicate that 99mTc BN is well labeled, stable and safe. Its distribution in normal subjects is similar to that of 111In octreotide, with the important difference that the spleen is not visualized. Absence of splenic uptake confirms the already known difference between the cellular distribution of BN and somatostatin receptors. No or insignificant uptake of the spleen is probably an advantage when the upper abdomen has to be studied. Colon cancer, exocrine pancreas cancer, as well as neuroendocrine gastroenteropancreatic tumors are candidates for detection with 99mTc BN because they show overexpression of BN receptors. 

Overexpression of BN receptors on SCLC and prostate cancer is well known and has been widely reported; however, its...
demonstration in humans with a non-invasive procedure is not trivial because the presence of receptors shown in vitro in tissues removed from the body does not automatically translate into the feasibility of an in vivo scan. From a diagnostic point of view, scintigraphic detection shows the extent of receptor-bearing tissue; it is simpler and quicker than pathological examination and does not depend on tissue sampling. Conversely, scintigraphic imaging may serve to guide biopsy sampling.

This is not the first time that the expression of BN receptors has been demonstrated by scintigraphy. However, we used a synthetic amphibian BN which is able to bind to all BN receptors present in mammals, albeit with varying affinity.4 In human tumors including prostate cancer three BN receptors have been identified. Of course, GRP shows more specific binding. Moreover, it is the first time that primary tumors have been detected with labeled BN, and – at least to our knowledge – that a primary prostate cancer has been imaged by scintigraphy.

Our report is still preliminary, and assessment of diagnostic parameters such as sensitivity and specificity will require further study on a larger number of patients. Nevertheless, our first results are encouraging. An important finding was that 99mTcBN showed more localizations of SCLC than sestamibi and was quickly taken up in the two cancers studied without any significant washout. SCLC can also be imaged with somatostatin receptors for bombesin/gastrin-releasing peptide; it will be interesting to study the differences, if any, between the uptake of these two receptor-seeking radiopharmaceuticals, as BN and somatostatin are antagonists and their receptor distribution is similar but not identical. The interest in 99mTcBN might also be important for radioguided biopsy and surgery, as well as for control of surgical radicality. In this respect 99mTcBN could be more useful in prostate cancer diagnosis and surgery than in SCLC, with is often inoperable.

References


RADIOGRAPHIC BIOPSY OF OSTEOMA OSTEOMA: USEFULNESS OF IMAGING PROBE

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Abstract

Aims and background: When removal of osteoid osteoma is performed with open biopsy, the surgeon can be guided by radioactivity of 99mTc-MDP (methylene D- phosphate) acquired by a probe. Material and methods: We compared the performance of a
commercially available ZnCdTe probe (Neoprobe 2000) and a one-square-inch-field-of-view imaging probe (IP) on two patients undergoing open biopsy for osteoid osteoma. Triphasic bone scintigraphy was performed before operation and Neoprobe as well as IP were used in the operating room by two nuclear physicians. When the surgeon asked for guidance, each nuclear physician had to indicate a precise direction. Results: The surgeon asked for guidance once in the first operation, on a patient with osteoid osteoma of the femur, and four times in the second operation, for osteoid osteoma of the acetabulum. The indications provided by IP were correct 5/5 times, whereas the commercial probe was correct 3/5 times. Both devices were able to assess the surgical radicality. After biopsy, bone samples were divided into high-count and low-count samples. Pathological examination confirmed the presence of osteoid osteoma in high-count samples. Conclusions: IP has already been used to guide biopsy, but only in breast disease. The present work confirms its good performance also in orthopedics as a portable mini gamma camera that can be used in the operating room.

Key words: bone scintigraphy, high-resolution scintigraphy, open biopsy, osteoid osteoma, position-sensitive photomultiplier tubes.

Introduction

Osteoid osteoma is a benign bone tumor whose complete removal means cure. Removal can be obtained with open or needle biopsy1,2. Both methods have their disadvantages and pitfalls3-5. Open biopsy is, though minor, a surgical procedure. Furthermore, osteoid osteoma is not easy to identify: diagnostic imaging methods such as CT, MRI and bone scintigraphy generally help surgeons to find the lesion1,2,6-9. Needle biopsy is a CT-guided method; the needle has to be brought exactly to the site where CT shows the lesion. Needle biopsy is less traumatic than open biopsy, but undesirable effects, mainly due to infection, may occur. With both methods there is a risk of incomplete tumor removal: when not completely excised, the core of the osteoma will regrow10,11. Since the last decade 99mTc-MDP has been used successfully to help surgeons during open biopsy. Detection of radioactivity is usually performed with a standard gamma probe for radioguided surgery, although mobile gamma cameras have also been employed12-16. Osteoid osteoma is generally well imaged with CT, MRI and bone scintigraphy; however, even in well-localized osteoma bone biopsy may be problematic and present the risk of incomplete excision. Radioguided biopsy has been used to help surgeons1. Standard probes may have limitations when other sources of radioactivity are present in their field of view. Our group has recently developed a miniaturized, portable 1-square-inch-field-of-view gamma camera, the IP, which was initially used for sentinel lymph node localization in breast cancer2,3. In the present study we used the IP together with a standard, commercially available probe for radioisotope localization of osteoid osteoma during biopsy procedures.

Material and methods

Patients

Two patients, scheduled to undergo surgical biopsy of osteoid osteoma that was diagnosed and localized with standard X-ray, MRI and CT, were operated on after having been given 240 MBq of 99mTc-MDP. In each patient triphasic and whole-body bone scintigraphy were performed before they entered the operating room. The standard probe with an acoustic signal and the IP were used contemporaneously to guide the surgeon to the lesions.

Equipment

The standard probe was a commercially available Neoprobe 2000 (Neoprobe, USA) with a zinc cadmium telluride crystal as the sensitive part, equipped with a standard tungsten collimator showing 25% angular resolution. The IP has been described elsewhere17. It is a miniature, high-resolution gamma camera whose low weight (~1 kg or less, depending on the prototype) and small size render it fully portable, also for use in the operating room. Any nuclear physician is able to use it after a short training period. Briefly, IP is composed of a one-square-inch-field-of-view Hamamatsu R7600 position-sensitive photomultiplier tube (PSPMT) coupled to a multicrystal array of $2 \times 2 \times 5$ mm$^3$ CsI (TI) (Hamamatsu, Japan); the device is fitted with a low-energy, general-purpose collimator (1.7 mm hexagonal hole). The IP we used was connected to a 500 MHz, Pentium III-powered portable PC. Electronics for PSPMT output readout, analog-to-digital conversion and by-hardware treatment of signals was designed by the research group in collaboration with Capodarco Electronics (Paliano, Italy) and CEA (Lauzacco, Italy). These companies also collaborated in the final assembly of the IP. Software for image treatment, including on-flow smoothing when required by the operator and variable pixel size/number on acquisition and display, was also homemade. IP and its parts have been described in detail in the literature.

Bone scan

Each patient was given 740 MBq of $99mTc$-MDP three hours before surgery. Dynamic and early static images (within 10 mins) were obtained of the skeletal segment where the osteoid osteoma had been visualized by CT and/or MRI. A whole body scan was performed 2.5 hours after injection. Subsequently, anterior, lateral or oblique views of the hot spot area were acquired to better define the position of the nidus within the sclerosis. The region of focal abnormality was localized with a fine radioactive marker and the skin was marked using a dermographic pen. ROIs were plotted on the hot spot area and adjacent bone region (background) to calculate the ratio between target and background area.

Radioguided surgery

In order to get to an osteoma it is necessary to create a breach through the bone. This breach is directed towards the tumor on the basis of computed tomography and/or magnetic resonance imaging. It is, however, not always easy for the surgeon to decide how to proceed from there. Nor is it always obvious whether the surgeon has actually identified the osteoid osteoma, because he has only his eyes and hands as diagnostic tools. Finally, it is not easy to establish whether all the osteoma has been removed. Bone scan shows higher than normal bone radioactivity in osteoma lesions. However, in order to help the surgeon, imaging will have to take place in the operating room. We tested the performance of the two probes at the beginning of biopsy and every time the orthopedic surgeon asked for guidance. The surgeon was invited to ask for guidance in a precise and dichotomous way, asking, for example, Is the osteoma ventral or cranial? The indications provided by the two probes were subsequently classified as right, wrong or not useful. The two probes were also used to detect residual activity after removal of the tumor. Removed bone samples were then sent to the pathologist who was unaware of the count rates of the samples.

Histology

Removed samples were classified as high-count samples and background samples and blindly sent to the pathologist, who examined them after standard hematoxylin-eosin staining.

Statistics

Counts obtained with the IP and the commercial probe were expressed as average ± standard deviation. Student’s t test was used when appropriate.
Results

Triphasic bone scintigraphy started visualizing the osteoid osteoma lesions in both patients at five minutes from injection. The lesions were well visualized also on two-hour images acquired just before the patients entered the operating room. One osteoid osteoma was located on the external femoral condyle of the left leg and the other close to the acetabulum. The tumor on the femoral condyle was easily found and the non-imaging as well as the imaging probe were used only at the beginning of surgery, once during surgery and at the end of surgery to ascertain the absence of radioactive peaks after tumor removal. The probes were also used to count the samples. The surgeon asked for radioisotope guidance four times during the second biopsy. The non-imaging probe was able to indicate the correct move in three out of five requests for guidance; once the probe was not able to give useful indications and once it gave a wrong indication. By contrast, IP correctly guided the surgeon five out of five times. During the search for the tumor IP always showed a clear hot spot; the image disappeared once the surgeon had removed all tumor tissue. Four of the 12 bone specimens, including bone removed to create the breach, showed high counts $\times 10^3 \times g^{-1}$ and eight showed low counts in the first patient. In the second patient three specimens showed high and 11 low counts. The osteoma/background ratio (O/B) measured on scintigraphy was 1.76 in the first patient and 1.57 in the second. The best O/B ratios with Neoprobe during surgery were 2.82 and 2.18, respectively, while the best O/B ratios with IP were 2.82 and 2.18, respectively, during surgery and at the end of surgery to ascertain the absence of radioactive peaks after tumor removal. The probes did not allow a more accurate search for the nidus with minimal removal. J Bone Joint Surg, 81: 814-820, 1999.


Discussion

Our preliminary data demonstrate the usefulness of IP in osteoid osteoma biopsies. Non-imaging probes have been used successfully and the present work does not deny the usefulness of the currently available probes but simply shows that IP is quicker and more precise in detecting osteoid osteoma, and thus probably more useful. The qualifier “probably” is mandatory because the method used to detect osteoid osteoma first with a conventional probe and then with IP does not allow a more accurate search for the tumor after the surgeon has realized he was on the wrong track. Moreover, only two patients were studied and both errors of the conventional probe occurred in the same patient, in whom interference with bladder activity might have produced Compton scatter interference. The performance of IP has been described in previous papers, mainly in relation to breast disease17,18. Orthopedic pathology is a typical field in which it is worth to test the usefulness of IP. Not only osteoid osteoma but also occult inflammation may be difficult to locate. Furthermore, the IP is able to ascertain the radicality of surgery, which is sometimes of crucial importance. In conclusion, this is the first time an IP has been used in orthopedics; our study has clearly demonstrated the usefulness and intriguing possibilities of this detector.
Abstract
A one-square-inch-field-of-view mini gamma camera, whose first prototype was built by us in 1998 and given the name imaging probe (IP), was initially employed in sentinel lymph node (SLN) detection. This is probably the best way of learning how to use it. In the present work IP was used for SLN localization by a medical team that, after having been trained by the group of nuclear physicians of “La Sapienza” University who designed and first used the detector, used IP at their own hospital to 1) acquire experience for future use during surgery (a cooperative project on IP-radioimaged orthopedic surgery is ongoing) and 2) start multicenter trials with IP. The SLN was identified and localized with IP and a non-imaging probe, Neoprobe 2000, in six patients with breast cancer who underwent lymphoscintigraphy for SLN biopsy. The operators who used Neoprobe and IP were blinded to each other’s findings and to the results obtained with the large-field-of-view Anger camera that was used for lymphoscintigraphy. The Anger camera, IP and Neoprobe detected seven SLNs in six patients. The mean detection time was 2 mins 6 s (standard deviation (SD) 26 s) with IP, and 2 mins 18 s (SD 47 s) with Neoprobe 2000. The SLN that was most difficult to find was detected in 2 mins 56 s with IP and 3 mins 45 s with Neoprobe. The operators’ subjective impression of having detected the SLN behind the skin mark was “absolutely sure” for 7/7 nodes with IP and “absolutely sure” for 5/7 nodes with Neoprobe.

Key words: breast cancer, high-resolution, lymphoscintigraphy, node biopsy position-sensitive photomultiplier tubes, scintigraphy.

Introduction
The one-square-inch-field-of-view camera is a fully portable, high-resolution mini gamma camera named IP whose basic features have been described elsewhere. Although the device was designed for intraoperative use, the earliest diagnostic images obtained by Scopinaro et al. depicted sentinel lymph nodes (SLNs) day before their surgical removal. In this setting the probe proved to be useful for identifying sentinel nodes that a large-field-of-view Anger camera failed to detect during lymphoscintigraphic imaging. When a surgical team starts working with IP, SLN localization is the ideal procedure for learning how to handle the probe, interpret its images, and use the software options in real diagnostic working conditions, although not with the speed and sterile conditions required during surgery. Preoperative SLN localization is a mandatory step in SLN biopsy. After localization a mark is drawn on the skin. When the surgeon starts operating the SLN behind the skin mark is checked with the aid of a portable radiation counter (probe); it is subsequently excited, counted to make sure the active node has been removed, and sent to the pathologist. Initial localization is generally performed with a large-field-of-view Anger camera whose images show the injection site and a second, less active source of radiation indicating a lymph node. This node is assumed to be the first node draining the tumor. Although in breast cancer the SLN is generally located in the ipsilateral axilla, when technetium-labeled colloids are injected close to the tumor, extra-axillary lymph nodes, such as subclavicular or even intrathoracic nodes of the internal mammary chain, may take up radiolabeled particles. Scopinaro et al. showed the very unusual presence of nodes very close to the site of injection, which had not been imaged with the Anger camera nor detected with conventional, non-imaging probes. Nieweg et al. also observed some cases in which it was very difficult to detect the SLN with the Anger camera and suggested the prone lateral view for localization. It should be remembered that difficulties in detecting the SLN are only encountered when the tracer is injected peritumorally and not when radiocolloids are injected subcutaneously in the upper outer quadrant of the breast. The aim of this work was to confirm that IP is able to detect SLNs in breast cancer without any increase in examination time. An additional aim was to start with the multicenter use of a new medical technology that requires a certain amount of training on patients before its full use in radioguided surgery.

Material and methods
Six breast cancer patients scheduled for breast-conserving surgery and SLN biopsy were given an injection of 99mTc Nanocoll (Nycomed-Amersham-Sorin, Saluggia, IT) 37 MBq in 0.2 cc saline close to the tumor under X-ray or ultrasound guidance the day before surgery. After injection of the tracer lymphoscintigraphy was performed with a 40-cm-field-of-view Anger camera (Starcam 4000 GE Mil, USA) fitted with a general-purpose, low-energy collimator and connected to a dedicated computer. Patients were placed as much as possible in the same position as during operation, ie anterior view and extended shoulder articulation. Before a skin mark was drawn on the projection of the SLN detected by Anger camera, two independent operators, one of whom had received a short training in SLN detection with IP, attempted to detect the SLN with a commercially available probe and with IP. Both operators were blinded to each other’s findings and to the Anger camera image. The time required for detection was measured and the operators themselves reported when the best possible detection was achieved. Furthermore, each operator had to state whether in his opinion node location was A) absolutely exact, B) probably exact or C) uncertain, but not better detectable. At the end of each procedure node localization with the probes was compared with the Anger camera images whose localization of the SLN was assumed to be correct and the projection of the SLN was drawn on the skin. Surgery was performed the following day. The SLN was removed and sent to the pathologist for microscopic examination according to previously described protocols.

Probes
The two probes we used in this study were a standard Neoprobe 2000 (Neoprobe, USA), kindly supplied by Ethicon Endo-Surgery, and the new IP. Neoprobe 2000 is well known and used worldwide. Briefly it consists of a 14-mm zinc cadmium telluride (Cd Te Zn) semiconductor crystal reusable collimated detector with internal tungsten shielding and an angular resolution of 25° with respect to the body of the probe. Although slightly modified, the IP was very similar to the prototypes previously described and used by our group. Briefly, it consists of a Hamamatsu R7600-00-C8 (Hamamatsu, Japan) position-sensitive photomultiplier tube (PSPMT) with charge readout electronics. R7600-00-C8 is a compact metal channel dynode photomultiplier tube with eight crossed plate anodes (4X + 4Y), ten multiplication stages, and nine metal channel dynodes followed by a reflective one. Eight preamplifiers are directly connected to each anode. PSPMT was matched with a multi-crystal array of 2.6 x 2.6 x 5 mm3 CsI (TI) crystals, similar to the arrays used in high-resolution cameras. External lead shielding was 8 mm thick, thicker than the shield of the first prototype. The collimator was a low-energy, general-purpose collimator with 1.5 mm hexagonal holes, 22 mm length, and 0.2 mm Pb septa (Nuclear Fields, Netherlands), quite similar to the collimators used in high-resolution scintimammography. Two circuits for weighted sum were built to evaluate the centroid of charge distribution. A National Instruments AT-MIO 6110E series card was used for analog-to-digital conversion. It was plugged into a docking station for an Asem 500 MHz Pentium III-powered portable PC. It was interfaced with the scintillation imager by a control unit board for event processing. Pulse height uniformity responses affect the overall energy resolution and the energy window selection. A look-up table
The LUT was built after acquisition of the flood field source with the IP. This LUT estimates the contribution of individual crystals to the total energy spectrum and to the image, thus allowing us to calculate individual gains from individual pulse height distribution and to correct heterogeneity in energy response. After correction, an energy window was selected and the resulting image was used as counting uniformity response. The acquisition and image processing software was developed using Graphics-Language Lab Windows C++ (National Instruments, USA.). To make the imaging device faster during localization of hot spots, the acquisition system is able to perform real-time imaging. Data made the imaging device faster during localization of hot spots, as for the operators’ opinion on the accuracy of detection the operator who used IP was absolutely sure (answer A) of his detection in 7/7 nodes, whereas the operator who used Neo-
probe 2000 was absolutely sure of five locations (answer A) and scored as “probably exact” the location of two nodes (answer B).

The SLNs were imaged by Anger camera as radioactivity spots without a defined shape. Smoothed high-resolution images obtained with IP showed an elliptical shape of four nodes whereas three nodes appeared quite circular. Two nodes, both imaged 20 mins after radiotracer administration, showed a kind of radioactive tail at one of their poles. This tail might represent the afferent lymph vessel.

**Discussion**

The first prototype of the IP was tested on SLNs. The working conditions with SLN identification are extreme: the injection site is a strong radiation source because interstitial lymph drainage is very slow; the radiation source it is generally placed on side of IP in working conditions. Scopinaro’s first experience led him to increase the lateral lead shielding. As in the first prototype, the electronics are fully contained in the probe used in this study, and the data can be sent directly to the portable PC. A further expected decrease in the size of the electronics will probably allow us to shorten the length of the probe, with a consequent reduction of its size and weight. In the present study, however, the size and weight of IP never presented any problems for handling by the nuclear physician. We wish to underline that our protocol for detecting the SLN with IP was different from other protocols whose aim it was to detect nodes that were not found with the Anger camera. The present protocol had no direct clinical utility: although the operators had received previous training, the present protocol was more similar to a training study than a diagnostic trial. Scopinaro et al. used IP to discover nodes that were missed by Anger camera or non-imaging probe, whereas here we only studied patients whose SLNs had previously been detected by Anger camera. However, some of the results are intriguing: although blinded to the Anger camera results, the nuclear physician who used IP was always absolutely sure of having detected the SLN, unlike the operator of the non-imaging probe. If these simple data would be confirmed in larger series, combined use of a large gamma camera and non-imaging probe could become useless in the future, since IP alone would be able to detect the SLN with the precision of the Anger camera and the mobility of a probe. This would also reduce the cost of the procedure. The average detection time was not significantly different between Neo 2000 and IP when Student’s t test was used; however, with IP the SD was much narrower than with the non-imaging probe. Interestingly, the longest detection time was needed for the same node with both types of probes. The detection time with Neo-probe was more than two SDs longer than the mean whereas the detection time with IP, although longer than its mean detection time, was within two SDs. This indicates that detection by IP is scarcely affected by node position. This could be important for hypothetical detection without large cameras and has the same meaning of a subjective absolute sureness of node detection acquired with IP. The final images obtained with IP had limited diagnostic interest: in the case of SLN localization no detailed image is needed when a radioactive hot spot in the vicinity of the injection site can only be a node or a bundle of lymph vessels. Lymph vessels disappear in 10 to 20 mins, allowing the Anger camera to check the node. The issue is completely different if we consider lymph node imaging as a feasibility task and a method to train physicians for using IP during surgery, where the shape of the image as well as the time of detection are important. During surgery it is often possible to place the IP, covered by a sterile cuff, on the suspicious lesion to acquire high-quality images.

In conclusion, acquisition with software allowing to change the pixel number and a fast smoothing program enables the IP user to quickly and accurately identify his target also in peculiar conditions.
conditions. Final high-resolution, high-quality images can be obtained after having centered the IP over the gamma ray source of interest, preferably by placing the IP on the target source. Training by experienced physicians is a prerequisite for correct use of IP. We confirm that SLN detection is the diagnostic method of choice for achieving good quality training.

References


CLINICAL USE OF AN IMAGING PROBE IN BREAST CANCER SURGERY

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Abstract

Aims: Portable cameras allow easy transfer of the detector, and thus of radioisotope imaging, to the operating room. In this paper we describe our preliminary experience in radionuclide imaging of breast cancer with a 22.8 × 22.8 mm2 field-of-view minicamera called “Imaging Probe” (IP). Methods: Breast cancer detection by IP was performed to guide biopsy, in particular open biopsy, or help fine-needle or core-needle positioning when the main guidance method was ultrasonography or digital radiography. 99mTc Sestamibi (MIBI) was injected 1 h before imaging and biopsy to 14 patients with suspected or known breast cancer. Scintigraphic images were acquired before and after biopsy in each patient. The surgeon was allowed to take into account scintigraphic images as well as previously performed mammograms and ultrasonography. Results: High-resolution IP images were able to guide biopsy toward cancer or toward washout zones of cancer, which are thought to be chemoresistant, in seven patients out of 10. Four patients in whom IP and MIBI were unable to guide biopsy were found not to have cancer. Conclusions: Our study confirms the ability of IP to guide breast biopsy even when our minicamera has to be handled manually by trained physicians during surgery.

Key words: breast cancer, high-resolution, lymphoscintigraphy, position-sensitive photomultiplier tubes, scintigraphy, sentinel node biopsy.

Introduction

Biopsy is the most accurate method to diagnose breast cancer because of its absolute specificity. The sensitivity depends on correct localization of the lesion: inadequate localization may result in tumors being missed, the need for repeated biopsy or, in the case of open biopsy, excessively invasive and time-consuming procedures. Biopsy is also useful for the biological characterization of cancer. For example, in locally advanced breast cancer neoadjuvant therapy is required to reduce the dimensions of large tumors; chemotherapy is generally based on anthracyclines, but some tumors are resistant to these drugs. Biopsy tells whether the tumor contains p-glycoprotein, obviously when a chemoresistant part of the tumor is included in the biopsy specimen. Biopsy is not the only procedure in which breast cancer must be localized: when breast-conserving surgery, the preferred approach to breast cancer in most cases nowadays, is planned, the surgeon has to be guided as rapidly as possible to the tumor and the surgical incision should be a small as possible. Several methods are currently used to guide surgeons to breast lesions. The major disadvantage of these methods is their invasiveness; lead markers, dyes etc. have to be inserted into the breast with a needle after localization of the tumor. Mammography and/or ultrasonography are the most frequently used techniques to locate cancer. Mechanical markers, the most widely employed method, are prone to displacement; moreover, the fine yarn that is inserted as a tracer from skin to lead bullet necessarily also guides the initial surgical incision, which does not always correspond to the surgeon’s plan. 99mTc MIBI has been used since 1993 as a breast cancer-seeking radio pharmaceutical1,2 and high-resolution scintimammography has
Recently been shown to be able to detect metabolic differences or other uptake differences within T1 breast cancer\(^1\). The Imaging Probe (IP) is a miniature gamma camera that was built and patented by us in 1997\(^4\) and has subsequently been modified and improved on the basis of our experience. We used it initially for sentinel lymph node detection\(^5,9\) and intraoperative localization of bone tumors. The aim of the present work was to investigate whether IP can be used for detecting and localizing breast cancer, inside and outside the operating room, in patients scheduled for MIBI scintimammography who previously received 20 mCi (740 MBq) of this widely accepted breast cancer-seeking agent.

### Material and methods

Ten patients with suspected breast cancer (average age, 57 years; range, 53-62 years) and four patients with locally advanced breast cancer (age range, 55-61 years) were studied with MIBI prone scintimammography for diagnostic purposes. In six of them final diagnoses were obtained with fine-needle biopsy, in five with US-guided core biopsy, and in three with open biopsy. The three patients who underwent open biopsy had undergone prone scintimammography four to seven days before the operation. They were given another injection of MIBI one hour before surgery and were studied with IP during surgery. All patients gave their written informed consent according to the rules of the local ethics committee.

#### Scintimammography

Ten to fifteen and 60-80 mins after injection of 740 MBq MIBI prone scintimammography was performed with a G.E. Millennium double-headed gamma camera (GE, USA) equipped with low-energy, general-purpose collimators. In patients with locally advanced breast cancer prone scintimammography was performed 10 mins after tracer injection and repeated at 1 h, 2 h and 3 h.

#### Imaging probe

High-resolution scintigraphy with IP was performed after standard 1-h scintimammography, with the woman sitting upright with her breasts resting on a shielded table. A lead shield was also placed over the thyroid. The nuclear physician gently compressed the breast in correspondence with the IP area. At the end of the first IP scintigraphy the circumference of the device was outlined with a dermographic pen on at least two points of the breast, so that it could be placed in the same position for subsequent acquisitions. High-resolution IP scintigraphy for open biopsy was performed with the IP in the hands of the surgeon as well as of the nuclear physician. However, intraoperatively acquired images were always interpreted by a trained nuclear physician with particular expertise in digital images and IP software.

IP has been described in detail in previous papers\(^6-11\). The main difference between the first prototype\(^6,10\) and the one used in the present study was its weight, which increased from 0.8 kg to 1.2 kg due to thicker lead housing and faster electronics. Briefly, the present IP detector module consisted of a parallel-hole collimator, a scintillation crystal array coupled to a compact PSPMT, charge readout electronics, and a PC-based acquisition and data processing system. To make the IP more effective during localization of hot spots, data processing was designed in such a way as to obtain real-time images during examination. The acquisition window on the PC normally shows two images: a “search image” containing all valid events in the refreshing time (minimum 0.9 seconds), and a “sum image” containing all valid events from the start of acquisition. Once the area containing the enhanced uptake was localized in the field of view, final acquisition could be started to obtain a final lesion “sum image”. During examination the IP images were available in gray or color scale. Although acquisition was performed on a 64 × 64 pixel frame, it was possible to view the images on 8 × 8 (crystal-array size) or 32 × 32 pixel frames, switching between with/without linear smoothing presentation.

### Results

Ten of 14 patients with suspicious lesions on mammography or ultrasonography showed X-ray opacities and four showed microlcifications. One mammogram was partially dense, but the opacity was clearly visualized. Ultrasonography detected lesions in 10 patients, including four with large cancers. Ten of the 14 suspicious lesions were proved to be cancers, three lesions were fibroadenomas, whereas in one patient no benign or malignant breast disease was found. The final diagnoses were obtained by fine-needle biopsy in seven patients, open biopsy in three and core biopsy in four patients. Of the four patients with locally advanced cancer two showed immunohistochemical staining for MDR products and two were negative in this respect. Prone scintimammography with an Anger camera was clearly positive in eight patients, weakly positive or probably negative in four patients, and definitely negative in two. In one case biopsy was guided only by IP. In this case, a T1b cancer, prone scintimammography failed to clearly image the tumor and ultrasonography was of no help to the surgeon. IP had difficulty detecting MIBI washout from chemoresistant or partially chemoresistant breast cancers. In all these cases the tumors were larger than the field of view of IP, with a very high degree of scattered radiation. However, in two patients a washout area was detected by IP and the biopsy was directed towards this area following marking of the skin. Biopsy was positive for MDR gene products.

### Discussion

Breast biopsy was directly guided by imaging of MIBI uptake with IP in one patient. IP can be used in the operating room, whereas Anger cameras cannot. Covered with a sterile plastic sheet, IP can be brought into close contact with the tumor. Of course, ultrasonography can also be used in the operating room but does not always provide accurate imaging that is useful to the surgeon. Lead markers or dyes can be introduced under X-ray guidance but sometimes it is not clear where they should be placed, or, as happened in one of our patients, the marker may be dislocated in the interval (24 h in our patient) between insertion and biopsy. It was an important finding that in one patient out of ten, or more appropriately one out of three, the only method guiding the surgeon was IP. In another six biopsies radioisotope guidance took place indirectly. Although the needle was not guided to the tumor only by means of scintigraphy, the radiotracer was nevertheless able to guide it toward the most metabolic part of the lesions.

Localization of breast cancer is a prerequisite for biopsy. Radiotracers such as MIBI are able to detect breast cancer\(^1,12-13\), with some limitations but also advantages with respect to morphological techniques. IP is a high-resolution device and compression is mandatory in high-resolution imaging: the thinner the radiation source, the greater is the advantage of high resolution\(^10,14,15\). In fact, the best scintigraphic images with a high-resolution device have been obtained of leaves of green plants\(^15\). IP can be positioned in such a way as to obtain gentle compression of the breast. Such compression is not painful because it involves only a small area and can be considered as displacement of tissues rather than compression. During surgery IP can be brought into close contact with the tumor, theoretically excluding any background noise. However, in this preliminary trial in clinical practice our tumor-seeking device failed to detect two small cancers out of 10 and was inconclusive in detecting two washout areas of MIBI. It should be taken into consideration that we worked without a mechanical arm to stabilize IP and that it is very difficult to hold
In a fixed position for more than 30 seconds. On the other hand, our previous experience with the 0.8 kg prototype taught us that its external shielding was too easily crossed by lateral rays. The current 1.2 kg device is adequately shielded but more difficult to handle. Furthermore, the use of MIBI means that the chest is a vast source of gamma rays; hence small shifts in the detection angle between IP and the breast may dramatically increase the background. We believe that an appropriate holding arm will be of great help in improving the performance of IP. The design of this arm is not a trivial matter; however, this is outside the range of the present discussion.

Washout detection needs some extra comment: in this case IP is surrounded by high-uptake tissue. This worsens the detected spectrum as well as the image. Moreover, to place IP at exactly the same position for subsequent acquisitions is a cumbersome procedure. Lastly, although this was not so obvious in the present study, the IP performance at present depends on the presence of trained nuclear physicians: this was mandatory in our experience.

Although not without limitations, IP has shown its usefulness: open biopsy had never before been guided by radiotracer. One biopsy in the present study was guided entirely by IP. Tumors sized 1 cm or less showed inhomogeneous uptake, as we had expected but never actually observed. Software allowing rapid changes of pixel size as well as on-line smoothing helped the nuclear physician to quickly reach the tumor during surgery. In the operating room IP was more specific than conventional scintigraphy. Moreover, to place IP at exactly the presence of significant hot spots in two patients, whereas in the third pathologist. Biopsy samples were counted by IP before they were sent to the X-ray stereotactic biopsy system dedicated to direct the mammotome needle taking advantage of a new, dedicated gamma camera. Eur J Nucl Med, 26: 1279-1288, 1999.


NEW LOCALIZATION TECHNIQUE FOR BREAST CANCER BIOPSY: MAMMOTOME GUIDANCE WITH IMAGING PROBE

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Abstract

Aims and background: The “Imaging probe” (IP) is a small, portable, high-resolution gamma camera to be used in radioguided surgery. The present work discusses a special prototype designed for guiding biopsies. The IP was mounted to a Fischer digital X-ray stereotactic core biopsy system in such a way that biopsy could be guided simultaneously by X-ray stereotaxis and 99mTc-Sestamibi (MIBI) images from IP. Methods: The IP field of view was 22.8 x 22.8 mm², with a spatial resolution of approx. 2.5 mm. We used off-line software for image fusion on a dedicated Pentium III portable PC. It was matched with a Fischer digital X-ray stereotactic biopsy system dedicated to direct the mammotome towards breast opacities. The operator was allowed to slightly correct the direction of the mammotome needle taking into account stereotactic X-ray, scintigraphic and fused images. Biopsy samples were counted by IP before they were sent to the pathologist. Results: High-resolution IP scintigraphy showed substantial, though not exact, matching between MIBI hot spots and X-ray opacities. More than one hot spot was detected even in the smallest (0.6 cm) lesion. Post-biopsy scintigraphy showed absence of significant hot spots in two patients, whereas in the third patient one of the three hot spots was still partially present. All
lesions showed cancer on histological examination. **Conclusions:** Measurement of radioactivity in biopsy specimens confirmed the heterogeneous distribution of radioactivity within cancers that IP had detected before biopsy.

**Key words:** biopsy, breast cancer, high-resolution scintigraphy, position-sensitive photomultiplier tubes, sestamibi.

**Introduction**

Core biopsy is the most widely accepted method to reach a diagnosis of breast cancer because of its almost absolute specificity. Its sensitivity depends on the accuracy of biopsy needle guidance towards suspicious tissue. The best validated guidance method is stereotactic digital X-ray mammography; the biopsy needle is semiautomatically directed toward the opacity, whose depth was previously calculated by computer on the basis of three-projection digital mammography. Limitations of stereotactic biopsy are the presence of X-ray-occult cancers, occurrence of multiple opacities, and scars from previous biopsies. **99mTc-Sestamibi scintimammography** is much more specific than X-ray mammography. The sensitivity, which is unsatisfactory for lesions smaller than 1 cm with Anger camera scintimammography, rises to 80% or more when scintimammography is performed with high-resolution detectors and under compression. Moreover, high-resolution scintimammography is able to show metabolic inhomogeneities within breast tumors. This is important because tumors generally do not develop isotropically: some cell clones are more aggressive than others and sometimes the inner part of a tumor is necrotic. Small-field-of-view, high-resolution cameras (PATENTS No. US 6,232,609B1 and US 6,242,744 B1), such as the imaging probe (IP), when used together with a stereotactic digital X-ray device might therefore substantially improve the accuracy of stereotactic needle guidance. Our pilot study was aimed at validating the combined use of high-resolution scintimammography using the high-resolution IP and stereotaxis for needle guidance in breast biopsy.

**Material and methods**

Our study involved three patients scheduled for mammotome core biopsy; they had suspicious breast opacities with a major axis of 0.6, 0.8 and 1.5 cm, respectively. Biopsies were performed with a mammotome system mounted to a Fischer prone stereotactic biopsy table (Fischer Imaging, Denver, Colorado, US) equipped with an X-ray tube giving multiple projections at 0, -15 and +15 degrees. The highest sample was applied when the operator had to modify the position of the mammotome, so that pre- and post-biopsy scintigraphic images were comparable.

To roughly identify the sample showing the maximum uptake, IP was used as a simple counter. Due to the small sample size (about 1 cm length, 2 mm diameter) and activity, the LEAP collimator was dismounted from IP and biopsy samples were counted by subtracting the background activity. Samples were then weighted and specific activities were calculated. Standard histology was carried out for final pathological diagnosis, starting with the hottest sample.

**Results**

X-ray and scintigraphic images obtained in the same geometric conditions showed different precision in determining the exact position of each sample (maximum distance about 1 mm). Thus spatial correction, although small, was necessary to calculate coordinates in experimental conditions, for example when X-ray and IP images had to be fused. The same correction was applied when the operator had to modify the position of the sample on the mammatome system. The tumors of all three patients showed MIBI uptake within or in close vicinity to the X-ray opacities. Focal uptake of MIBI never perfectly matched the shape of the opacities. At least two distinct hot spots were found in the 6- and 8-mm opacities, and three spots in the lesion measuring 15 mm. In all three cases the operator selected a target point between, as equidistant as possible, the two most active spots. Scintigraphic images acquired after biopsy showed breast background activity in two patients and a spot of residual uptake in the third patient. The ratio between the count rate of the whole background activity and the LEAP parallel-hole lead collimator (Van Mullekom, NL) showing hexagonal holes of 1.5 mm width, 22 mm length and 0.2 mm septa. The charge readout electronics consist of eight preamplifiers directly connected to each anode. Two weighted summing circuits were built to produce signals related to the X and Y positions. Summing circuits produce two signals related to the total charge collected by X and Y anodes (Capodaro Elettronica, Italy). The acquisition system is based on an analog-to-digital converter PCI-6110E card (National Instruments, USA) plugged into a 500 MHz Pentium III Assem portable PC. Data acquisition and image processing software was developed using Graphics-Language (LabWindows by National Instruments). The spatial resolution of IP is 2.5 mm FWHM according to laboratory tests and the sensitivity at 99mTc photon energy is 600 cpm/μCi (1 μCi = 37 kBq). Scintigraphic and digital X-ray images showed different dimensions and geometric references. In order to fuse these images IP was previously calibrated using scintigraphic and digital X-ray images obtained from a simple five-parallel-hole lead phantom. Calibration of X-ray and scintigraphic systems allows to compute exact coordinates, phase (angular coordinates) and zoom factor. A 0-degree-projection digital X-ray image was acquired. This image for X-ray calibration was downloaded from the Fischer system, utilizing Matrox Inspector 3.0 software. The acquired image in X-ray calibrate mode was DICOM 1024 × 1024 pixel 16-bit gray scale resolution. Good quality scintigraphic and X-ray images of the same phantom were superimposed to check the coordinates of the holes. The scintigraphic image was first obtained on an 8 × 8 pixel frame and then expanded to 64 × 64 pixels by linear smoothing. Lastly, the image was recorded in bitmap mode. A geometric reference was obtained by superimposing the images acquired using scintigraphic and radiological methods under the same conditions. 740 MBq of 99mTc-MIBI was injected to each patient approximately 1 h before biopsy. Scintigraphic images corresponding to 50 s acquisitions were stored on 64 × 64 pixel frames using on-line smoothing software. A second – offline – software application was used to fuse X-ray with IP scintigraphic images. The operator, who had to choose the exact point to which the mammotome should be directed, could look at scintigraphic, X-ray stereotactic and fused images simultaneously. Post-biopsy scintigraphic and as well as stereotactic X-ray images were acquired. In the second scintigraphy IP was positioned at exactly the same place and distance from the breast as before biopsy, so that pre- and post-biopsy scintigraphic images were comparable.

**Discussion**

The ability of IP to guide biopsy as well as the ability of high-resolution MIBI scintimammography to detect inhomogeneous distribution of MIBI within breast tumors have already
been demonstrated and discussed by us. The present study confirms both observations. Image fusion with digital X-ray stereotactic mammography is a valuable step ahead in the field of radioisotope-assisted biopsy. The technique used by us seems to be satisfactory for this application because the size of the field of view is well suited for breast lesions scheduled for biopsy. Various improvements are possible: an acquisition time of 50 seconds gives good images but can be prolonged because the weight of the IP, which at presents limits the acquisition time because the operator has to hold the IP, will no longer be a problem when the IP is mounted to the stereotactic core biopsy system. The software can be further improved and we are working on that too. However, the software of the present IP shows major improvements with respect to the previously described prototypes9-11. Other parts of the device underwent only minor changes. The present prototype is reliable, although its performance in terms of counting efficiency can probably also be improved. Our results with breast biopsy will have to be validated in larger series; this will allow us to discover the pitfalls of the technique reported here. The absence of benign lesions in our very small series is obviously a limitation; however, this was only a pilot study. It is worth noting that our method of image fusion provides semiautomatic IP-MIBI guidance of mammotome biopsy. The results of future biopsies will be directly comparable with data of the present pilot series. Another limitation of the present work is the absence of histochemical data on angiogenesis. Although scintigraphic images, after counting of removed specimens and the pathological finding of tumor tissue in the high-count samples, confirmed the inhomogeneous distribution of MIBI within tumors2, histochemistry could be used to interpret the nature of the inhomogeneous uptake. It is particularly important to understand whether this depends on inhomogeneous distribution of cancer tissue, with less activity in areas of fibrosis, necrosis or hemorrhage, or on the presence of more intense neangiogenesis, as suggested in previous works11-13, or more aggressive cell clones. The IP is an attractive tool that is ready for clinical testing in those applications where simple counters are currently used. Moreover, new radiopharmaceuticals able to create higher tumor-to-background ratios will possibly augment the usefulness of IP.

References

LYMPHATIC MAPPING AND SENTINEL NODE IDENTIFICATION IN SQUAMOUS CELL CARCINOMA AND MELANOMA OF THE HEAD AND NECK

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Aim: The aim of our study was to evaluate the role of scintigraphy in lymphatic mapping and in the identification of the sentinel lymph node (SLN) in patients with head and neck cancer. Methods: Between September 1999 and February 2001 we enrolled 22 consecutive patients with cancer in the head and neck region: five squamous cell carcinomas, one Merkel cell tumor of the cheek and 16 malignant melanomas. Lymphoscintigraphy was performed three hours before surgery after injection of 30-50 MBq of 99mTe-Nanocoll in 0.3 mL; the dose was fractionated by injecting the radiotracer at two points around the lesion. Static acquisition (anterior and/or lateral views, 512 x 512 matrix, 5 mins pre-set time) was started immediately after the injections so as to visualize the pathways of lymphatic drainage. The skin projection of the SLN was marked with ink. Intraoperative SLN detection was performed with perilesional injection of patent blue. Results: SLNs were found with lymphoscintigraphy in all patients. Thirty-three SLNs were identified: one occipital node, three nodes at the base of the tongue, 10 superficial lateral nodes (external jugular), five submandibular nodes, five submental nodes, three mastoid nodes and six supraclavicular nodes. Biopsy was performed in 21/22 patients. In 20/22 patients the first lymph nodes were visualized in the proximal cranial regions (retroauricular, jugular and submandibular) at five minutes post injection. The location of the SLN was 13.6% (three patients). All patients with tumor-positive SLNs were submitted to radical dissection. Poor concordance in the detection of sentinel nodes was observed with patent blue. Conclusions: The flow of nanocoll in the lymph vessels of the head is rapid. In our experience immediate
scintigraphic imaging was essential to visualize the pathways of lymphatic drainage and the first SLN. Radioguided SLN biopsy is therefore recommended within three hours. Injection of patent blue is inadvisable because of the poor concordance with lymphoscintigraphy and the risk of permanent tattooing of the face.

Key words: head and neck, lymphoscintigraphy, malignant melanoma, sentinel node, squamous cell carcinoma.

Introduction

The lymphatic system of the head and neck has different physical and anatomical characteristics from that of the rest of the body. The lymph vessels have more valves and form a network of communicating links, which is more complex and articulated than any other part of the body. With gravity the lymph flows in a cranio-caudal direction towards the great veins in the neck, reaching the internal jugular-subclavicular junction.

The technique of lymphatic mapping has to be adapted to the highest speed of the lymphatic flow. Sentinel lymph node (SLN) biopsy is an accurate and non-invasive method for the diagnosis of metastatic disease and has a valid prognostic role with respect to the spread of lymph node micrometastases. Tumor staging can be aided by excision of the SLN; in fact, this is the current method used for the selection of T2-T3 melanoma patients for radical lymphadenectomy. SLN examination may provide the indication for lymphadenectomy in patients with a high risk of other tumor types.

In our department we have extended the use of lymphatic mapping and SLN identification to patients with squamous cell carcinomas (SCC) of the oral cavity. In the US about 15,000 new cases of oral cavity SCC are diagnosed each year and the introduction of rational criteria for the selection of patients for radical neck dissection would be a solution to the perceived needs of all those involved. The five-year disease-free survival rate for oral cancer is about 40%.

The chances of cure depend on the oral subsite involved and the clinical stage of the disease. The presence or absence of regional lymph node metastases is the most important factor in the prognosis of patients with oral cancer. The cure rates for oral cancer are reduced by approximately 50% in patients with cervical lymph node metastases. Regional lymph node metastases occur in about 30% of oral cancer patients.

The current treatment for oral cancer is excision of the primary tumor followed by elective neck dissection and radiotherapy. However, this may result in many patients (about 70%) undergoing unnecessary and expensive radical treatment, with undesirable side effects, morbidity and scarring. The aim of our study was to evaluate the role of lymphoscintigraphy in lymphatic mapping and the prognostic value of SLN biopsy in patients with oral cavity SCC and head and neck melanoma.

Materials and methods

From September 1999 to February 2001 we enrolled 22 consecutive patients in our study: five with squamous cell carcinoma, one with a Merkel cell tumor of the cheek, and 26 with malignant melanoma of the head and neck. The melanoma patients underwent excisional biopsy of the primary lesion (margins 1-3 mm) for histological examination. The selection criterion for inclusion in our study was T2-T3N0M0 primary skin melanoma.

The radionuclide (99mTc-Nanocoll) was administered to patients with oral cavity SCC at two injection sites around the primary lesion. Within three hours the patients underwent surgical removal of the primary tumor and SLNs. All patients underwent radiographic and clinical examination for staging purposes and to exclude the presence of systemic macroscopic spread of the disease. Lymphoscintigraphy was performed three hours before surgery after injection of 30-50 MBq of 99mTc-Nanocoll (Nycomed, Amersham, Sorin) in 0.3 mL of saline solution; the dose was fractionated by injecting the radionuclide at two points around the primary lesion. Static image acquisition (anteroposterior oblique view, 512 x 512 matrix, 5 mins pre-set time) was started immediately after the injections to visualize the pathways of lymphatic drainage. The skin projection of the first node was marked with ink. For intraoperative detection of the SLN we administered a perilesional injection of patent blue to each patient.

Results

Lymphoscintigraphy revealed SLNs in all patients. We were able to identify 33 SLNs: one in the occipital region, three deep cervical nodes at the base of the tongue, 10 external jugular nodes, five submandibular nodes, five submental nodes, three nodes in the mastoid region and six in the supraclavicular region.

Radioguided biopsy was performed in 21/22 patients. In 20/22 patients the first lymph node with its afferent vessel was detected in the proximal cranial region (retroauricular, jugular and submandibular) within five minutes of radionuclide injection. By prolonging the scintigraphic acquisition time some more minutes (15-20 mins), we were able to observe rapid diffusion of the radionuclide through the efferent lymphatics to the deep cervical nodes or to the supraclavicular region. The percentage of micrometastases in the SLNs was 13.6% (three patients). All patients with positive SLNs underwent radical neck dissection.

The use of dyes revealed only a slight relationship between the stain and the radionuclide due to the brief persistence of the dye in the sentinel nodes.

Discussion

The lymphatic flow in the head and neck vessels is faster than in other parts of the body, which is confirmed by scintigraphic data which have shown in many cases that the radionuclide, consisting of microcolloid particles of human albumin marked with technetium of a diameter of about 80 microns, after having passed the SLNs moves faster towards the other lymph nodes. However, a small amount of the radionuclide will remain in the first SLN for three to six hours, which is sufficient to perform a radioguided biopsy. The use of dyes in head and neck lymphatic mapping is of little practical use because of the rapid lymphatic washout. Patent blue may not remain in the SLN long enough for surgery to be performed. Moreover, there is often poor concordance with scintigraphic data and there is a risk of permanent tattooing.

We started scintigraphy immediately after injection of the radionuclide. This allows precise identification of the first SLN and visualization of the lymphatic drainage of the tumors by following the initial pathway of the radionuclide. Prolongation of scintigraphy allows to detect the efferent lymphatic route and to identify the second, distal SLN.

On the basis of our experience we recommend radioguided SLN biopsy to be performed within three hours of injection of the radionuclide. The use of SLN biopsies is of particular clinical interest in patients with SCC since this tumor is characterized by marked local invasiveness and about 20-50% of patients develop regional lymph node metastases.

Accurate identification of one or two SLNs using our method in SCC patients with primary tumors of the buccal floor and lips was successful in all cases. Furthermore, radioguided SLN biopsy reduces morbidity as well as time and cost, it results in an improved aesthetic outcome, and has rationalized the use of the available therapeutic resources.

At 12 months follow-up SLN-negative patients with SCC had no signs of recurrence or metastatic spread. With longer follow-up we will be able to clarify the prognostic role of this method.
In melanoma, where SLN biopsies have been used for a longer period, the prognostic value seems to be high.

References

Aims and background: Gastrinomas are the most common neuroendocrine tumors of the duodenum. Gastrinomas may be primary or metastatic. The primary type of radical treatment is the primary type of radical treatment.

Methods and study design
A 65-year-old obese male (weight >100 kg) had been surgically treated for an acute peritonitis from perforation of the first jejunal loop, with laboratory values indicating elevated gastrin levels in the blood (800 pg/mL; normal value up to 100 pg/mL) while esophagogastroduodenoscopy (EGDS), ultrasonography and MRI were negative. In our institute the patient was submitted to selective celiac-mesenteric angiography which revealed a hypervascularized mass of 1 cm in diameter at the descending part of the duodenum (Figure 1). Scintigraphy with labeled octreotide confirmed the presence of this lesion and revealed a second lesion located in the left thyroid lobe (Figures 2 and 3). Radioguided surgical removal of both lesions was performed following iv administration of 120 mBq In-pentetreotide 20 hours before surgery. This method confirmed the diagnosis and revealed another uptake area of 1 cm in diameter near the uncinate process of the pancreas. The combined use of intravenous contrast material for the pancreas and the mesenteric axis (Figures 4 and 5). Histological examination demonstrated a low-grade, highly differentiated duodenal gastrinoma, together with lymph node metastasis and nodular hyperplasia of the thyroid.

Results
Total surgical excision is the ideal treatment for sporadic gastrinoma because it reduces the incidence of metastasis and improves quality of life and survival time, with a modest percentage of complications and practically zero mortality. However, surgical treatment may not be applicable in the presence of metastases. Medical treatment is being reevaluated for such cases, especially considering the relatively slow growth of these tumors. Identification of a polyendocrine MEN1 syndrome may lead to re-evaluation of the therapeutic approach, given the difficulty of designing a radical treatment strategy in relation to the multifocal nature of the lesion. A fundamental aspect in the diagnosis and treatment of gastrinomas and of endocrine tumors in general is the localization of the tumor. Common imaging methods are unable to identify lesions smaller than 1 cm and have relatively low
sensitivity (CT 43%, US 36%, arteriography 68%). They are therefore not very useful in the identification of primary pancreatic and duodenal tumors, and even less in the case of possible liver and lymph node metastases. Recently, endoscopic ultrasonography and labeled octreotide scintigraphy have proved to be particularly effective. In particular Octreoscan, scintigraphy with \(^{111}\text{In-DPTA-phe-octreotide (pentetreotide), has a sensitivity}\) ranging between 62% and 90%, identifying lesions which had not been identified by other methods in 28% of cases. Intraoperative ultrasonography, gastroscopy for duodenal transillumination, and repeated blood gastrin determination also after inhibition tests with secretin should be adopted in the surgical treatment of gastrinomas, as is already being done in neuroendocrine tumors of the duodenal-pancreatic region.

**Conclusions**

The clinical application of radioguided surgery in cases of tracer-uptaking endocrine tumors remains controversial. In our case the decision to use this method was influenced by the fear that the pa-
tient’s obesity and the effects of previous surgery would hamper the identification of the small tumor. This method helped us avoid use-
less and potentially risky dissemination of neoplastic cells. More-
over, one or more intraoperative histological examinations might have prolonged surgery, leading to further risks. The final result was a precise and oncologically radical surgical resection, aimed at preventing early relapse without the risk of a blind mass resection.

References


SENTINEL LYMPH NODE DETECTION BY LYMPHOSCINTIGRAPHY IN MALIGNANT MELANOMA

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Abstract

Aim and background: Sentinel lymph node (SLN) detection is currently employed in patients with malignant melanoma (MM) to spare them unnecessary lymph node dissection. Methods and study design: We investigated 241 patients (130 men and 111 women, median age, 50 years (range, 14-92)) with MM (192 before and 51 after surgical biopsy); two of them had more than one melanoma lesion. In each patient approx. 10 MBq of 99mTc Nanocoll in 0.1 mL (Nycomed Amersham Sorin; particle size range, 3-80 nm) was injected intradermally around the MM lesion or surgical scar. Dynamic acquisition was performed for 20 minutes (20 frames/min) and the study was concluded within four hours of injection. Using an external radioactive marker, the skin over the SLN was marked with China ink. Results: 294 SLNs were scintigraphically identified: 117 in the inguinal region, 147 in the axillae, four in the submandibular region, three in the laterocervical region and 23 at other sites. In two patients no drainage was detected. In 43 patients more than one sentinel node was identified. In 13 patients with lesions located in the trunk the tracer drained towards multiple lymph node stations or unexpected lymph nodes (nine cases). Histology and immunohis-
tochemistry diagnosed MM in 25 SLNs; 19 were positive for metastasis with hematoxylin-eosin staining, five with HMB45 and one with CD68 immunostaining. All 25 detected lymphatic basins were excised. In nine of these basins there was metastatic involvement of at least one other lymph node besides the SLN. During follow-up, which ranged from six to 86 months, metastatic disease was found in only one patient with a histologically negative SLN six months after surgery. Conclusions: This study confirms the utility of scintigraphic SLN detection in patients with MM. In most of the cases the procedure led the surgeon to evaluate the drainage area, which is unpredictable for lesions in the trunk and may be difficult to delineate using only patent blue dye. Furthermore, in approximately 10% of cases we observed dual drainage from individual lesions, mainly those located on the trunk. We will proceed to compare the results obtained during follow-up with those of an investigational group of patients with melanoma who were not subjected to lymphoscintigraphy for SLN detection in order to obtain well-founded information on the prognostic value of this technique.

Key words: lymphoscintigraphy, melanoma, sentinel node.

Introduction

Identification of locoregional lymph node metastases is crucial for the staging and prognosis of patients with malignancies 1-3. The most important prognostic factor in patients with malignant melanoma (MM) is metastatic involvement of locoregional lymph nodes. Decreasing the five-year overall survival to 40%. Other data such as Clark level, Breslow thickness and ulceration are less relevant. Most of these patients (90%) have a clinically limited lesion without locoregional or distant lymph node metastases 4. About 15-35% of patients with cutaneous melanoma at clinically stage I may develop metastases 4.

Several studies have confirmed that metastatic lymph node in-
volvement is sequentially organized rather than unpredictable. Almost 20% of patients with MM at diagnosis show metastatic involvement of locoregional lymph nodes even if the nodes are clinically negative. The overall five-year survival in patients with micrometastases is approximately 50%; it may decrease to about 30% in the presence of lymph node involvement. The presence of occult tumor cells in patients at clinical stage I makes elective lymph node dissection (ELND) mandatory.

That it is now possible to identify patients with metastatic lymph nodes during diagnosis is clearly the merit of lymphoscintigraphy. Morton et al. introduced the concept of the sen-
tinel lymph node in 1992. This concept is based on the assump-
tion that each cutaneous region drains to a well-defined lymphat-
ic basin and that the first nodes in the basin are the sentinel lymph nodes (SLN) 1-4. Moreover, the chance of skip metastasis (the first lymph node in the basin is tumor negative but the sec-
ond node is tumor positive) is low (1-3%). SLN detection is a specific and sensitive procedure that has been accepted as a reli-
able, safe and less invasive diagnostic method. With the use of this method it is possible to identify patients with melanoma mi-
crometastases in the lymph nodes who should undergo elective lymph node dissection (ELND)\(^1\).

Materials and methods

From June 1994 to September 2001, 241 patients with melanoma were enrolled in the study (130 men and 111 women with a median age of 50 years; range, 14-92 years). One hundred ninety-two primary lesions and 51 scars of previous surgical excisions were studied. We identified 49 lesions with a thickness of <0.76 mm, 87 between 0.76 and 1.5 mm, 89 between 1.5 and 4 mm, one of 44 mm and five of unknown thickness.

Lymphoscintigraphy was performed 15-18 hours before surgery using a large-field-of-view rectangular gamma camera with a 20% window, equipped with a high-resolution, parallel-hole collimator for low energy. Four intradermal injections with \(^{99m}\)Tc colloidal albumin (10-30 MBq in 0.1 mL, particle size ranging from 3-80 nm) were administered around the lesion or surgical scar (0.5 cm from the border of the lesion). The injection sites were labeled with an indelible marker so that the same injection method could be used for intraoperative mapping with patent blue dye. Twenty minutes' dynamic acquisition (20 frames: 1/min, 64*64 matrix) was performed immediately after the four perilesional injections. Subsequently, static images were obtained in anterior and lateral projection to define the exact location of the SLN. If no lymph nodes were visualized, delayed images were acquired up to four hours post injection. Both acquisition and labeling were carried out with the patient in the surgical position. The intraoperative use of a vital dye (Patent blue V, 0.6-3.3 mL) injected into the perilesional or surgical scar derma about 20 minutes before surgery allowed us to evaluate the agreement between lymphoscintigraphic and chromatic data. A gamma probe was used for SLN identification (Neoprobe, Neo 2000 gamma detection system; energy range, 27-364 Kev). The primary lesion and the identified lymph node were examined. When pathological examination of the SLN was positive for micrometastases, the patient was scheduled for elective lymph node dissection. The SLN was examined using hematoxylin-eosin staining and immunohistochemistry (monoclonal antibodies against S-100 protein and the melanoma antigen associated with Hmb45). The non-SLNs removed in patients who underwent lymph node dissection were examined with the same methods used for SLN examination. Follow-up ranged from three to 86 months; patients underwent follow-up visits in the outpatient plastic surgery clinic with special attention being paid to the presence of local relapses, lymph node metastases and systemic metastases.

Results

The primary melanoma was located on the upper limbs in 26 patients (10.8%), on the lower limbs in 84 patients (34.8%), on the trunk in 117 patients (48.5%), and in the head and neck region in 12 patients (5%). Two patients (0.8%) had two lesions (left thigh and back in one case, right arm and left foot in the other).

Two hundred ninety-four sentinel lymph nodes were identified by lymphoscintigraphy. The SLN sites were the following: inguinal (117 cases; 39.8%), axillary (147 cases; 50%), submandibular (four cases 1.4%), laterocervical (three cases; 1%), and other sites (23 cases; 7.8%). Two patients who had previously undergone an excisional biopsy did not show drainage of the radioabeled compound, and the SLN could be identified only with vital dye. One SLN was detected in 196 patients (81%), two SLNs were found in 34 patients (14%), three in seven patients (3%), four in one patient (0.4%) and five in one patient (0.4%). Twenty-five of the 294 SLNs showed melanoma metastases: 19 were positive with hematoxylin-eosin staining, five with Hmb45 and one with CD68 immunostaining. All 25 lymphatic basins were dissected. In 16 basins the other lymph nodes were negative for metastasis, while in nine basins there was metastatic involvement of at least one other lymph node in addition to the SLN. The relationship between the number of metastatic SLNs and primary lesion thickness is reported in Table 1. Only one patient out of 49 with a Breslow index <0.76 mm had a metastatic SLN. Micrometastases in the SLN occurred more frequently in patients with a melanoma thickness between 1 and 4 mm (15/88; 17%). These data are in agreement with those reported in the literature. All patients underwent follow-up visits every three months for a period varying from six to 87 months. Among the histologically SLN-negative patients eight (3.7%) developed metastases and one patient died, while in the group of SLN-positive patients eight (32%) developed metastases and three died due to disease progression.

Discussion

Detection of the SLN by lymphoscintigraphy is important, particularly when the primary lesion is located on the trunk. This method detects the lymph node region of first drainage, which in many cases turns out to be different from the one expected by the surgeon. In agreement with the data reported in the literature, also in our experience in 13 patients with lesions located on the trunk the tracer drained towards more lymph node stations or unexpected lymph nodes (nine cases). This is very important for correct planning of surgery. In these cases dynamic acquisition was useful for the recognition of multiple lymphatic pathways, for differentiation of SLNs from non-SLNs, and for selection of the number and the correct set of lymph nodes for biopsy.

The value of histological examination of SLNs performed according to current techniques is very important, as shown also by our experience, because it influences the therapeutic course of these patients. Any antibody by itself is able to differentiate a benign from a malignant lesion, but same antibodies (S-100 protein, HMB 45, Mel 1, KBA.62, NK1 beteb, A/MART1, etc.) can be useful, if appropriately interpreted, for the histopathological diagnosis.

Follow-up of patients with malignant cutaneous melanoma is necessary for the early detection of relapse. Unfortunately only few studies have compared different schedules and frequencies of follow-up and their impact on survival. In every patient the follow-up schedule was planned in relation to the thickness of the primary melanoma, independent of the status of the sentinel node. The follow-up of patients with melanomas of less than 1 mm thickness was planned on an annual basis. Patients with primary melanomas >1 mm were examined every four months for the first three years and every six months until the fifth year. Clinical examination was accompanied by ultrasonographic examination of the potentially involved nodal regions and instrumental investigations were required in the presence of symptoms.

<table>
<thead>
<tr>
<th>Tumor thickness (mm)</th>
<th>No. patients (total)</th>
<th>No. patients with positive nodes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.76</td>
<td>49</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0.76 – 1.5</td>
<td>86</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>1.5 – 4</td>
<td>88</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>&gt;4</td>
<td>13</td>
<td>5</td>
<td>38.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>241</td>
<td>25</td>
<td>10.5</td>
</tr>
</tbody>
</table>

---

Table 1 - Relationship between metastatic SLN and primary lesion thickness
or specific risk factors. In our study metastases were more frequent in patients with positive SLNs (32%) than in patients with negative SLNs (3.7%) and the first site of relapse was more often in the locoregional lymph nodes than elsewhere. We intend to compare the results obtained during follow-up with those of an investigational group of melanoma patients who were not subjected to lymphoscintigraphy for SLN detection, in order to obtain well-founded information on the prognostic value of this technique.

References

MINIMAL SENTINEL NODE PROCEDURE FOR STAGING EARLY BREAST CANCER
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Abstract
Aims and background: Sentinel lymph node dissection (SLND) has recently been evaluated as a new staging technique for early breast cancer. To minimize the extent of surgery, the feasibility of eradicating primary breast lesions and the relative sentinel lymph nodes (SLN) under regional anesthesia was evaluated in this study. Methods and study design: A selected population of 76 patients with suspected operable breast cancer and no clinically palpable lymph nodes was enrolled in the study. Intra- and perileisional administration of a radiotracer was performed. Lymphoscintigraphy was carried out to confirm the drainage pathway and locate the SLN. The following day, after inducing a nervous block induction of the ipsilateral intercostal nerves, we performed the surgical procedure with the help of a hand-held gamma-detecting probe. In case the primary lesion was diagnosed as invasive carcinoma by frozen section, the SLN and the remaining axillary lymph nodes (non-SLNs) were removed. The status of SLN and non-SLNs was compared. Results: The primary breast lesion was located and excised in all cases (identification rate: 100%). Lymphoscintigraphy positively identified SLNs in 40/45 (89%) patients; in five patients no lymphatic drainage was detected. In 38 cases an average of 1.5 SLNs and 14 non-SLNs per patient were removed and pathologically analyzed; the remaining two patients showed SLNs in the internal mammary chain, which were not excised. Twenty-nine percent of the patients showed metastatic disease in the lymph nodes examined. Of all patients with affected nodes, 55% had cancer cells only in the SLN. No false negatives (skip metastases) were found. No immediate or long-term anesthesia-related complications (e.g. pleural lesions, intravascular injection) were observed. Conclusions: Our data confirm the feasibility of single radiotracer administration for both occult lesion and SLN localization as well as the usefulness of SLND in staging early breast cancer. Regional anesthesia resulted in easy management and good patient compliance. This time-saving procedure allowed the completion of the whole surgical plan, reducing the recovery time without modifying the effectiveness of surgery.

Key words: breast cancer, breast lesions, regional anesthesia, ROLL, sentinel node.

Introduction
Ongoing improvements in mammographic and sonographic screening have allowed the detection of early breast lesions including carcinomas, generally resulting in a more favorable prognosis with a significant reduction in the absolute mortality rate.

In patients with early breast cancer axillary lymph node metastasis is the most important prognostic factor for recurrence and survival and represents the basis for important therapeutic decisions. However, axillary lymph node dissection is associated with acute and chronic morbidity, and therefore a new minimally invasive procedure, sentinel lymph node dissection (SLND), has recently been evaluated as a new staging technique for early breast cancer.

It is well known from the literature that SLND allows to predict the status of the axillary lymph nodes in almost 98% of breast carcinoma patients. Radio-occult lesion localization, the so-called ROLL procedure, has been used to identify and remove both benign and malignant breast lesions.

The aim of the present study was to evaluate the feasibility of combining ROLL and SLND using regional anesthesia and single radiotracer injection in order to minimize the extent of surgery.

Patients and methods
Seventy-six women (mean age, 54 years, range, 34-76 years) with palpable or non-palpable small (≤ 2 cm) breast lesions documented by mammography and/or ultrasonography and with no clinically palpable lymph nodes were enrolled in the present study. Intra- and perileisional administration of a radiotracer (0.1 mL intra +0.1 mL peri of Nanocoll® [Amersham Sorin, Saluggia-TO; Italy]) labeled with 0.8 mCi 99mTc was performed. Lymphoscintigraphy was carried out 30, 60 and 180 minutes after radiotracer administration in order to confirm the drainage pathway and locate the SLN. The following day, after induction of a nervous block of the ipsilateral intercostal nerves with Ribovacaine, a surgical procedure with the help of a hand-held gamma-detecting probe (Neo-probe 1000®, Columbus, Ohio, USA) was performed.
When frozen section revealed a benign lesion or non-invasive carcinoma the surgical plan was stopped; conversely, when frozen section revealed invasive carcinoma the SLND and the remaining axillary nodes (non-SLNs) were removed and a quadrantectomy was performed under regional anesthesia. Each SLN and all the related non-SLNs were tagged separately and then submitted for definitive histological assessment including comparison of the status of the SLN and non-SLNs.

Results

Histological examination identified 45 invasive carcinomas among 76 breast lesions; the invasive tumors were staged as pT1 (2 pT1a; 11 pT1b; 32 pT1c). Of the remaining 31 cases, 24 proved to be ductal carcinoma in situ and seven were fibroadenomas (Table 1). All primary breast lesions were easily located under radioguidance (identification rate 100%) and subsequently excised. Lymphoscintigraphy identified the SLN in 40/45 (89%) carcinoma patients; in five patients no lymphatic drainage was detected. In 38 patients an average of 1.5 SLNs and 14 non-SLNs per patient were removed and examined by the pathologist. The remaining two patients showed SLNs in the internal mammary chain; in accordance with our protocol guidelines, these lymph nodes were not excised.

As seen in Table 2, routine hematoxylin-eosin examination of the SLNs accurately predicted the status of the non-SLNs in the rest of axilla (accuracy 84%). Twenty-nine percent of the patients showed metastatic disease in the lymph nodes examined. Of all patients with affected nodes, 55% had cancer cells only in the SLN. No false negatives (skip metastases) were found.

No immediate or long-term anesthesia-related complications (eg pleural lesions or intravascular injection) occurred.

Discussion

The feasibility of combining ROLL and SLND using a single injection of radiolabeled nanocolloid (delivered intra- and perilesionally) has been demonstrated by the present study. Every injection of radiolabeled nanocolloid (delivered intra- and perileSIONAL) occurred.

In conclusion, the combined ROLL-SLND procedure under regional anesthesia for both benign and malignant breast lesions allowed easy management and good patient compliance, reducing the recovery time without modifying the effectiveness of surgery. The standard surgical treatment of the axilla in patients with early breast cancer is undergoing a radical change: sentinel lymph node biopsy will be rapidly adopted in many centers worldwide. Nevertheless, it is important to underline that more data from randomized trials are required before SLND can be recommended as the new standard for breast cancer care.

Table 1 - Breast lesion characteristics

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>No. pts</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrating carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>2</td>
<td>ROLL + SLND</td>
</tr>
<tr>
<td>T1b</td>
<td>11</td>
<td>ROLL + SLND</td>
</tr>
<tr>
<td>T1c</td>
<td>32</td>
<td>ROLL + SLND</td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
<td>24</td>
<td>ROLL</td>
</tr>
<tr>
<td>Fibroadenomas</td>
<td>7</td>
<td>ROLL</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

ROLL: radio occult lesion localization; SLND: sentinel lymph node dissection.

Table 2 - Histological correlation between sentinel lymph node and axillary non-sentinel lymph nodes

<table>
<thead>
<tr>
<th>SLN</th>
<th>Non-SLN</th>
<th>No. pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEG</td>
<td>NEG</td>
<td>27 / 38</td>
<td>71</td>
</tr>
<tr>
<td>POS</td>
<td>POS</td>
<td>5 / 38</td>
<td>13</td>
</tr>
<tr>
<td>POS</td>
<td>NEG</td>
<td>6 / 38</td>
<td>16</td>
</tr>
<tr>
<td>NEG (false negative)</td>
<td>POS</td>
<td>0 / 38</td>
<td>0</td>
</tr>
</tbody>
</table>

SLN: sentinel lymph node; NEG: negative; POS: positive.

References

10. Nieweg OE, Kaptein BA, Petersen JL, Rutgers EJ, Van Dongen JA,
Lymph node involvement is frequent in differentiated thyroid cancer. It ranges from 33.5% to 53% in papillary thyroid cancer and is roughly 14% in follicular thyroid cancer\(^1\)-\(^3\). Although associated with a greater risk of local recurrence and lung metastases\(^4\), lymph node involvement is not considered an adverse prognostic indicator of death\(^5\).

Precautionary locoregional lymph node dissection in thyroid carcinomas for diagnostic and/or staging purposes is useless both in differentiated (papillary and follicular) and undifferentiated forms, where it does not improve the prognosis\(^5\). It is only indicated in medullary carcinomas because of their frequent spread to regional lymph nodes, and in this case will include the lymph nodes of the central compartment (paralaryngeal, inferior laryngeal, and anterosuperior mediastinal lymph nodes).

Various types of lymphadenectomy can be distinguished:

- **Node-picking**: removal of clinically suspect lymph nodes.
- **Ablation of the central compartment**: excision of the perithyroid lymph nodes.
- **Functional dissection or modified radical dissection (MND)**: excision of the lymph nodes of the central compartment and the laterocervical district.
- **Radical dissection (RND)**: en bloc resection of all regional lymph nodes of the neck.
- **Cervical and mediastinal lymphadenectomy**: excision of the cellular-lymphatic tissue and of the anterosuperior mediastinal lymph nodes.

The objective of lymphadenectomy is to contain tumor spread; however, the procedure may be associated with intraoperative complications and postoperative sequelae. In order to improve the therapeutic management of patients with thyroid carcinoma, diagnostic scintigraphy with \(^{201}\text{TI}\) or \(^{99m}\text{Tc}\)-sestamibi is used in the advanced and undifferentiated forms of this tumor\(^5\). In view of the clinical experience acquired by use of the intraoperative radiodetection of nodal lesions of different regions, we describe the application of this technique to the clinical case discussed below.

### Materials and methods

We treated a 72-year-old woman who had undergone a total thyroidectomy for papillary carcinoma (pT3) without subsequent radiometabolic treatment. On physical examination we noticed a swelling on the left side of the neck. The lesion was confirmed by ultrasonography, CT scan, and scintigraphic examination with \(^{99m}\text{Tc}\)-sestamibi 24 hours before planned lymphadenectomy. During the surgical procedure we performed radiodetection to localize metastatic lesions. **Results**: Intraoperative radiodetection may help to identify residual disease, which is often difficult to trace in the presence of post-surgical fibrosis. In our patient, histological examination of the removed tissue specimens demonstrated that intraoperative radiodetection had been highly accurate. The eradication of residual disease was confirmed by scintigraphic follow-up after 12 months. **Discussion and conclusions**: Scintigraphy with \(^{99m}\text{Tc}\)-sestamibi has been proposed as a means to localize metastatic spread and possible residual disease after a supposedly radical thyroidectomy. Surgical eradication of all residual tumor guarantees the best disease control without having to resort to radiometabolic therapy. This approach will reduce the incidence of iatrogenic morbidity and consequently improve the patients’ quality of life.

**Key words**: lymph node metastasis, medullary thyroid carcinoma, radioguided surgery.

### Introduction

Lymph node involvement is frequent in differentiated thyroid cancer. It ranges from 33.5% to 53% in papillary thyroid cancer and is roughly 14% in follicular thyroid cancer\(^1\)-\(^3\). Although associated with a greater risk of local recurrence and lung metastases\(^4\), lymph node involvement is not considered an adverse prognostic indicator of death\(^5\).
demonstrated that intraoperative radiolocalization had been highly accurate. The eradication of residual disease was confirmed by scintigraphic follow-up after 12 months.

Discussion and conclusions

Scintigraphy with $^{99m}$Tc-sestamibi has been proposed as a means to localize metastatic spread and possible residual disease after a supposedly radical thyroidectomy. Moreover, sentinel lymph node detection in thyroid neoplasms may detect non-palpable nodal metastasis and local recurrences just as easily as in melanoma and breast cancer. The technique can also be performed in concomitance with the administration of iodized contrast medium for further diagnostic imaging.

Surgical eradication of all residual tumor guarantees the best disease control without having to resort to radionuclide therapy and allows the clinician to base follow-up only on the measurement of thyroglobulin levels. This approach will reduce the incidence of iatrogenic morbidity and consequently improve the patients' quality of life.

References


DAY-SURGICAL MANAGEMENT OF DUCTAL CARCINOMA IN SITU (DCIS) OF THE BREAST USING WIDE LOCAL EXCISION WITH SENTINEL NODE BIOPSY

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Key words: day surgery, DCIS, sentinel node biopsy.

Introduction

Various studies have shown sentinel node biopsy (SLNB) to be an accurate method of assessing the status of the axillary lymph nodes in patients with early-stage breast cancer. There are several advantages of SLNB with wide local excision over traditional axillary dissection: a less invasive surgical procedure, elimination of postoperative drainage of the axilla, less discomfort to the patient, and decreased incidence of lymphedema or neurovascular injury. SLNB with wide local excision can often be performed in an outpatient setting without the use of general anesthesia.

Methods

This technique was employed in 24 patients; the average age was 54.5 years (range, 34-75 years). All patients were scheduled to undergo surgery on an ambulatory basis; patients entered day surgery 2-4 h after injection of the radiocolloid in the nuclear medicine suite for lymphoscintigraphy.

The technique involves intra- and peritumoral injection of an average of 1 ml technetium-labeled colloid. Paravertebral block was performed in the preoperative holding area with hemodynamic and pulse oximetry monitoring. Intradermal Carbocaina 2% was used at the site of needle dissection. The superior aspect of the spinous process above the nerve to be blocked was located and the overlying skin marked. The patient was then transferred to the operating room. The whole surgical procedure (SLNB and tumor resection with margins larger than 1 cm) included frozen section analysis to confirm the preoperative fine needle aspiration result. Intravenous antibiotic prophylaxis was given preoperatively. Intraoperative sedation was provided by infusion of Dripvan. Intraoperative features analyzed included tumor location, tumor palpability and frozen sections obtained. The histological features evaluated included tumor size, estrogen and progesterone receptor status, axillary lymph node metastases and associated non-infiltrating ductal carcinoma in situ.

Patients were evaluated in the recovery room with regard to fitness for discharge. Oral antibiotics were prescribed until drain removal. Before discharge, patients were given oral and written instructions on wound and drain care and expected drainage output. Patients were seen at the outpatient clinic within 10 days of discharge and thereafter as needed for wound examination and consultation with radiation and medical oncologists. Drains were removed when the output was less than 30 ml a day.

Results

The operative time averaged 75 minutes for wide local excision with SLNB. There were no intraoperative complications. Pathological analysis revealed the presence of malignancy in all excision specimens. All 24 cases were confirmed to be DCIS; in three cases microinvasion was present. The primary lesions were located and excised in all cases (identification rate 100%). Lymphoscintigraphy identified the SLN in 22 of the 24 (91.6%) patients; in two patients no lymphatic drainage was seen. In 20 cases the SLNs were excised and submitted to pathological examination; the remaining two SLNs were located in the internal mammary chain and therefore not excised. Two of the 24 patients had positive SLNs, one was only cytokeratin positive and the other was both hematoxylin and eosin and cytokeratin positive. The patients with occult micrometastatic disease to the SLN underwent complete axillary lymph node dissection, and the SLNs were the only nodes found to have metastatic involvement.

Twenty of 24 patients rated the overall surgical, anesthetic, and recovery experience as “very satisfactory”. Patients typically expressed pleasure at the ability to return home and stressed the ease of recovery. Those who had prior experience with general anesthesia expressed a distinct preference for paravertebral block. Patients scheduled for day surgery were discharged after an average stay in the recovery room of two hours. All patients who underwent planned admission for postoperative observation
were discharged the morning following surgery, and one patient was discharged within four hours of surgery. Nausea and vomiting complicated the recovery of three patients who were subsequently admitted to the recovery room for control of nausea and intravenous fluids. They had no further episodes of nausea or vomiting. One patient with incomplete paravertebral block required intravenous administration of narcotics in the recovery room, eventually resulting in unplanned admission overnight for observation and pain control.

Discussion

Our results indicate that sentinel node biopsy and wide local excision associated with truncular or paravertebral block are a significant step forward in the search for less aggressive treatments for early breast cancer. The surgical approach to DCIS has become more conservative, and breast-conserving surgery is now considered an acceptable alternative to modified radical mastectomy in many patients. The management of the axilla in patients with DCIS with microinvasion is currently a point of debate. It has been generally accepted that axillary lymph node dissection is not indicated for DCIS patients because of the low likelihood of axillary node involvement. The chance of recurrence eight years after diagnosis was 7.5%, with a 1.4% risk of death from breast cancer. About 40% of low-grade lesions become invasive over a period of 25 to 30 years if left untreated. Approximately half of all local recurrences become invasive. Current treatments range from tumor excision to mastectomy. The width of the disease-free margin in the excised tissue is the most important factor in prognosis. Several studies have indicated that the chance of recurrence is smallest if tumor-free margins of at least 10 mm are achieved. The role of radiotherapy following excision has become controversial. Although earlier studies clearly indicated an improved prognosis with postoperative radiotherapy, there is now considerable interest in subgroups of patients in whom the advantages of radiotherapy may be outweighed by side effects, costs and adverse factors. In particular, radiotherapy may change the texture of breast tissue, thus complicating mammographic detection of recurrence. Decisions about the extent of surgery and the use of radiotherapy must be made on an individual basis.

Various local and regional anesthetic techniques have been described for breast surgery and are currently promoted as alternatives to general anesthesia. Specific techniques, however, may have their drawbacks. Field block and infiltration of a local anesthetic were first used for breast biopsy in the 1960s and have subsequently been accepted that axillary lymph node dissection is not indicated for DCIS patients because of the low likelihood of axillary node involvement.

References


SENTINEL LYMPHADENECTOMY IN CUTANEOUS MELANOMA

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Abstract

Aims and background: In the last ten years validation of the sentinel lymph node (SLN) concept has led to modification of the surgical approach for patients with intermediate-risk cutaneous melanoma. Methods and study design: Forty-eight patients affected by cutaneous melanoma with a Breslow thickness between 0.65 and 4 mm were enrolled in the study. Approximately 2 mCi of radiotracer and 1 mL of vital blue dye were injected in each patient around the site of the primary lesion. Lymphoscintigraphy was performed until the lymphatic basin and the respective SLN were localized. The whole surgical procedure consisted of enlargement of the surgical margins followed by localization and excision of the SLN(s) by using both radiotracer and vital dye. Whenever the SLN proved to be histologically positive for metastasis, complete regional lymphadenectomy was performed. Results: Within 15 minutes of radiotracer administration the lymphatic basin was localized in all 48 patients by lymphoscintigraphy. Vital dye and radiotracer successfully allowed SLN localization and excision in 46 of 48 patients (97%); in one case the SLN was detected by radiotracer alone. The SLN proved to be metastatic in six (13%) of 46 evaluable patients; interestingly, in three of them the presence of metastatic cells was revealed only by immunohistochemistry. All patients with tumor-positive SLNs had primary lesions with a Breslow thickness \( \leq 2 \) mm. Conclusions: Sentinel lymphadenectomy is able to identify lymph node involvement in patients with cutaneous melanoma with a Breslow thickness \( >1 \) mm, thus avoiding the risks associated with radical regional lymphadenectomy. Lymphoscintigraphy proved to be an important tool to obtain correct preoperative localization of the drainage basin, especially for melanomas located on the face and trunk.

Key words: melanoma, sentinel lymphadenectomy.

Introduction

In the last ten years validation of the sentinel lymph node (SLN) concept has led to radical modification of the surgical approach for patients with cutaneous melanoma with a Breslow thickness \( >0.75 \) mm\(^{-1} \). Lymph node staging in this group can be accomplished by prophylactic or therapeutic lymphadenectomy. However, the former, if performed indiscriminately, will overtreat patients with a relatively low risk of metastatic disease. In fact, radical regional lymphadenectomy is an invasive procedure associated with the risk of several complications including lymphedema, vascular lesions and nerve lesions. Conversely, therapeutic lymphadenectomy might undertreat a group of patients with preclinical lymph node involvement who may benefit from radical treatment. Sentinel lymphadenectomy, first introduced by Cabanas to stage penile carcinomas and subsequently developed by Morton, has been proposed to obtain correct staging but avoiding the above-mentioned complications.

Materials and methods

Forty-eight patients (mean age, 47 years; range, 17-73), 21 males and 27 females, affected by cutaneous melanoma with a Breslow thickness between 0.65 and 4 mm were enrolled in this study after having provided their signed informed consent. Twelve to eighteen hours prior to surgery 0.4-0.8 mL of Nanocoll (Amersham-Sorin, Saluggia, TO, Italy) radio labeled with approximately 2 mCi of \(^{99m}\)Tc as a radiotracer was injected around the scar in every patient. Planar bidimensional lymphoscintigraphic acquisition was started five minutes after injection in order to visualize the site of administration and any early drainage. From then on images were acquired every 10 minutes until clear identification of the lymphatic basin and the respective SLN was attained. The cutaneous projection of the SLN was marked on the patient’s skin.

The following day, 5-10 minutes before surgery, 1 mL of vital blue dye as a second tracer was injected around the scar. The surgical procedure started with external radio localization of the SLN by means of a hand-held gamma detecting probe, considering significant a SLN/background (BKG) count ratio \( >5 \). BKG counts were obtained at a fair distance from the drainage pathway. An incision over the cutaneous radioactive area of interest helped to locate the hot SLN and establish if it was colored by the dye. Ex-vivo counts were obtained to check the excised SLN and the residual cavity was scanned to locate other SLNs. Each SLN was submitted to histopathological analysis by routine hematoxylin-eosin staining and immunohistochemistry (IHC) with the MAb S-100 and HMB 45. In patients with a tumor-positive SLN complete regional lymphadenectomy was performed.

Results

The sites of the primary lesion were the face in six patients (13%), trunk in 16 (33%), arm in three (7%), and legs and feet in 23 patients (47%). The Breslow thickness of the primary lesions was \( <1 \) mm in 12 patients (25%), 1-2 mm in 24 patients (50%), and 2-4 mm in 12 patients (25%) (Table 1). Within fifteen minutes of radiotracer administration the lymphatic drainage and the respective basins were localized in all 48 patients by lymphoscintigraphy. Interestingly, in six of the 22 patients with melanoma of the face and trunk the lymphatic basin was different from the one expected, while in three patients a double drainage pathway was visualized.

SLNs were intraoperatively localized and excised using the combination of radiotracer and vital dye in 45 of 48 patients (94%). In one patient (3%) the SLN was identified and excised by radiotracer guidance only. Overall, sentinel lymph node dissection (SLND) was carried out in 46 patients (success rate 97%), while complete regional lymphadenectomy was performed in the two remaining patients with melanoma of the trunk because of the failure of intraoperative SLN detection.

In the 46 evaluable patients a total of 49 lymphatic basins was localized; one SLN was removed from 43 (87%) and two SLNs from the remaining six basins (13%). All excised SLNs were tagged separately and analyzed. The SLN was metastatic in six patients (13%); in three of them the presence of metastatic cells was revealed only by IHC (Table 2). No more than one SLN per patient proved to be positive for metastatic disease. All patients with metastatic disease had a Breslow thickness of the primary lesion \( \leq 2 \) mm.

Discussion

Preoperative lymphoscintigraphy has been confirmed to be an important tool for accurate localization of the lymphatic basin.
Table 2 - SLN Identification and histological status

<table>
<thead>
<tr>
<th>SLN Identification</th>
<th>Histological Status</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ps with SLN identified by LSG</td>
<td>48</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Ps who underwent RLND*</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ps with SLN excised at surgery</td>
<td>46</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Ps with SLN -</td>
<td>40</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Ps with SLN + RLN +</td>
<td>6</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Ps with SLN + micro</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Ps: patients; SLN: sentinel lymph node; LSG: lymphoscintigraphy; RLND: radical lymphadenectomy; RLN: regional lymph nodes.

* because of the absence of intraoperative localization of the SLN.

References

7. Uren RF, Howman-Giles RB, Shaw HM, Thompson JF, McCarthy M Goss 1, MC Bosso 1, F Moro 1, and S Sandrucci 1

THE SENTINEL NODE IN ANAL CARCINOMA

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Aims and background: Anal cancer is a rare condition. The inguinal lymph nodes are the most common site of metastasis in this neoplasm. The inguinal lymph node status is an important prognostic indicator and the presence of metastases is an independent prognostic factor for local failure and overall mortality. Depending on the primary tumor size and histological differentiation, metastasis to superficial inguinal lymph nodes occurs in 15-25% of cases. Methods and study design: To evaluate the inguinal lymph node status we performed a search for the sentinel node in a female patient affected by squamous anal carcinoma. Results: Identification and examination of the sentinel node was positive and postoperative histology showed the presence of a lateral lymph node metastases. Conclusions: We suggest that examination of the sentinel node in anal cancer could be an efficient way to establish the inguinal lymph node status, which would help the clinician to plan and perform adequate treatment.

Key words: anal cancer, lymph node metastasis, sentinel node.

Introduction

Anal cancer is a relatively uncommon neoplasm accounting for only 3-4% of cancers of the large bowel below the peritoneal reflection, and less than 2% of all large bowel cancers. In a study performed by Peters and coworkers the majority of anal region cancers (63%) were of squamous cell origin, another 23% being transitional cell cloacogenic carcinomas. Adenocarcinomas account for about 7% of all anal tumors, with Paget’s disease (2%), basal cell carcinoma (2%) and melanoma (2%) being reported but uncommon.

Anal cancer is more common in women in most areas of the world, although cancer of the anal margin is more common in men. There is a rising incidence of anal cancer in the male homosexual population. An important study by Surawicz et al. reported that in homosexual men the incidence of anal cancer has been estimated to range from 25 to 37 per 100,000, against an annual incidence in the total US male population of 0.7 per 100,000. HPV is the presumed etiologic agent in this setting. Squamous cell cancer of the anus may occur in the anal canal, the lower rectum, or the perianal skin.

The anal margin is extremely well vascularized and has an extensive lymphatic system. The lymphatics drain into the inguinal nodes, the lateral pelvic nodes and the mesorectal nodes. Tumors below the anal verge drain primarily into the inguinal nodal system. The distal 5 cm of rectum and the anal canal to the anal verge drain primarily to the inguinal nodes, along the middle hemorrhoidal vessels to the lateral walls of the pelvis, and into the inferior mesenteric system. Lymph node metastases are almost always present in advanced anal cancer. In fact, the inguinal
lymph node status is an important prognostic indicator and the presence of lymph node metastases is an independent prognostic factor for local failure and overall mortality. Depending on primary tumor size and histological differentiation, metastasis to the superficial inguinal lymph nodes occurs in 15-25% of cases.

Since primary treatment of anal cancer is predominantly non-surgical, it is difficult to assess the lymph node status in these patients. This is compounded by the unpredictable pattern of lymphatic drainage as a result of the extensive lymphatic connections between the inguinal and pelvic lymph node basins. A solution could be the use of the sentinel node technique in the management of patients with anal carcinoma. After injection of a radio-pharmaceutical it is possible to detect the first lymph nodes draining the anal region. The identification of metastatic lymph nodes can have major implications for treatment. We performed the sentinel node technique in a female patient with anal cancer.

**Patient and methods**

A 62-year-old woman presented with anal pain and bleeding to the Surgical Oncology Department of the University of Turin. The patient was submitted to anoscopy, which revealed a mass located in the anal canal. A biopsy was performed resulting in a diagnosis of squamous anal cancer. There were no palpable inguinal lymph nodes. The patient was submitted to radiotherapy and chemotherapy as proposed by Nigro. Treatment led to complete resolution of the symptoms and subsequent biopsies confirmed the absence of cancer. Four months after the end of the treatment the patient presented with a palpable inguinal lymph node. To evaluate the nodal status a radiopharmaceutical was injected into the site of the previous cancer and lymphoscintigraphy was performed, showing bilateral drainage to both groins (Figure 1) with focal accumulation of radioactivity which was marked on the patient’s skin. This was followed by bilateral radio-guided lymphadenectomy under local anesthesia. The patient was discharged on the day of surgery.

**Results**

The postoperative course was uneventful. Histological examination showed the presence of bilateral inguinal lymph node metastases, confirming the result obtained with lymphoscintigraphy and the positivity of probe-guided surgery. The patient subsequently underwent radiotherapy to the groin region.

**Conclusions**

Anal cancer is a rare condition and for many years surgical excision by abdominoperineal resection has been the standard treatment. In the 1920s and 1930s inguinal node dissection was included in the surgical management of these patients. In the 1950s it became evident that the morbidity associated with lymph node dissection was much greater than any survival benefit and the procedure was therefore abandoned.

Since 1974 multimodality treatment consisting of a combination of irradiation and chemotherapy has been the standard of care. However, it must be kept in mind that inguinal lymph node status is an important prognostic factor and the presence of inguinal lymph node metastases is an independent prognostic factor for local failure and overall mortality. This means that detection and examination of the sentinel node in anal cancer is fundamental for adequate management. The case presented here demonstrates that sentinel node identification in anal cancer is a feasible procedure that may allow the detection of metastatic nodes which are tumor-negative at clinical examination. Since the procedure can be performed in day surgery we recommend assessment of the sentinel node in all patients affected by anal cancer. However, further studies are required to confirm these results.

**References**


**SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER: THE GIVOM EXPERIENCE IN VENETO, ITALY**

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**Acknowledgments:** This study was financially supported by the Fondazione della Cassa di Risparmio di Padova e Rovigo.

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**Key words:** breast cancer, sentinel node.

**Introduction**

Sentinel node biopsy (SLNB) is a recently developed method to obtain information on the axillary lymph node status in breast cancer patients while avoiding the morbidity associated with standard axillary lymph node dissection (ALND)¹². The GIVOM (Gruppo Interdisciplinare Veneto di Oncologia Mammaria) investigated the reliability of this method in axillary staging by performing SLNB followed by ALND in 126 patients with breast cancer and comparing the histological findings in sentinel nodes with those in the other axillary nodes. The concordance rate was 95.6% and the false negative rate 10.9%: in five cases the sentinel nodes were tumor-negative but metastases were found in other axillary nodes. In all similar studies that have been performed worldwide false negative cases have been reported⁴⁶. The prognostic impact of false negative cases is still an open

![Figure 1 - Lymphoscintigraphy 75 mins and 2 h 30 mins after tracer injection.](image)
question, as this aspect has not yet been investigated in large randomized clinical trials. However, there are surgeons who now routinely perform SLNB rather than ALND in breast cancer patients with clinically negative axillae.

In view of the importance of evidence-based medicine, GIVOM members believe that there is a need for clinical trials comparing the therapeutic efficacy of SLNB with that of traditional ALND, and have therefore started a multicenter randomized trial involving 12 centers in the Veneto region of Italy.

Material and methods

Patients

Patients with invasive breast cancer with a diameter up to 3 cm and clinically negative axillae were considered eligible. Exclusion criteria were intraductal carcinoma, multicentric tumors, non-palpable tumors, clinically positive axilla, distant metastases, neoadjuvant treatment, pregnancy, and age over 80 years. Fully informed consent was required before patient randomization.

Study design

Patients were randomized to two arms. The first arm underwent SLNB followed by standard ALND; sentinel nodes were examined only by definitive histology. The second arm underwent SLNB with frozen section examination: if the sentinel node was negative no further surgery was performed, while if it was positive ALND was performed. If the sentinel node was negative at frozen section examination but positive at definitive histology, a delayed ALND was performed. Patients underwent postoperative treatment, including chemotherapy, to prevent metastases.

Surgical procedure

Surgeons had to have performed at least 15 consecutive SLNBs with ALND without false negatives before joining the trial. The sentinel node, identified by a gamma detecting probe in a sterile glove, was excised and the axilla was checked for residual radioactivity; each residual node with a probe count >10% of that of the most radioactive node was considered an accessory sentinel node and therefore excised.

Histopathology

For frozen section examination, nodes ≥0.5 cm were bisected while nodes >0.5 cm were sectioned each 2-3 mm. For each sample two frozen sections made at 40-µm intervals were examined. The frozen tissue was then thawed, fixed and embedded to obtain permanent sections.

For definitive histology, two consecutive 5-mm-thick tissue sections were cut from a paraffin block at three levels, each 40 mm apart. One of the two sections obtained from each of the three levels was stained with hematoxylin-eosin. Immunohistochemical analysis was performed on the remaining sections using a monoclonal antibody to cytokeratin.

Results

So far, 490 patients have been randomized, 248 to the first and 242 to the second arm. Thirty-eight patients were not eligible because they were found to have multicentric, intraductal or benign tumors. There have been 16 cases of protocol violation because patients did not undergo the treatment assigned. On evaluating the primary tumor features in the 384 cases considered, the distribution in the two arms appeared to be well balanced (Table 1). Tumors were T1a in 11/384 cases, T1b in 86/384, T1c in 225/384 and T2 in 62/384 cases. Histological grade was G1 in 79/384 cases, G2 in 191/384 and G3 in 114/384 cases. Sentinel nodes were found intraoperatively in 359/384 cases (93.5%). In 202/359 (56.3%) cases we found only one sentinel node, in 124/359 (34.5%) two and in 33/359 (9.2%) three or more. Sentinel nodes were found to be metastatic at definitive histology in 82/359 cases (22.8%) (Table 2). Frozen section examination of sentinel nodes was performed only in the second arm: in 10 of the 208 cases evaluated the sentinel node was negative at frozen section histology but positive at definitive histological examination. Therefore the concordance between intraoperative and definitive histological examination was 95.2%, with a false negative rate of 18.5% (10/54).

Discussion

The results reported in the several available phase I-II studies on SLNB were encouraging and consistent, although different technical procedures were used. SLNB prevents the morbidity associated with systematic ALND, the intraoperative identification rate of sentinel nodes is high, the method is sensitive for axillary staging and allows accurate diagnosis of nodal micrometastases. However, all authors have reported false negative results. This is an open question since it is not known whether understaging and

### Table 1 - Primary tumor characteristics

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Arm I (n = 189)</th>
<th>Arm II (n = 195)</th>
<th>Total (n = 384)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>4</td>
<td>2.1%</td>
<td>7</td>
</tr>
<tr>
<td>T1b</td>
<td>42</td>
<td>22.2%</td>
<td>44</td>
</tr>
<tr>
<td>T1c</td>
<td>115</td>
<td>60.9%</td>
<td>110</td>
</tr>
<tr>
<td>T2</td>
<td>28</td>
<td>14.8%</td>
<td>34</td>
</tr>
<tr>
<td>G1</td>
<td>40</td>
<td>21.1%</td>
<td>39</td>
</tr>
<tr>
<td>G2</td>
<td>95</td>
<td>50.3%</td>
<td>96</td>
</tr>
<tr>
<td>G3</td>
<td>54</td>
<td>28.6%</td>
<td>60</td>
</tr>
</tbody>
</table>

### Table 2 - Characteristics of sentinel lymph nodes (SLN)

<table>
<thead>
<tr>
<th>SLN Identification</th>
<th>Arm I (n = 189)</th>
<th>Arm II (n = 195)</th>
<th>Total (n = 384)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>176</td>
<td>93.1%</td>
<td>93.9%</td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>6.9%</td>
<td>6.1%</td>
</tr>
<tr>
<td>No. SLNs</td>
<td>1</td>
<td>64.8%</td>
<td>48.1%</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>29.0%</td>
<td>39.9%</td>
</tr>
<tr>
<td>≥3</td>
<td>11</td>
<td>6.2%</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SLN Metastases</th>
<th>Arm I (n = 189)</th>
<th>Arm II (n = 195)</th>
<th>Total (n = 384)</th>
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<tbody>
<tr>
<td>Yes</td>
<td>39</td>
<td>22.1%</td>
<td>25.1%</td>
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possible undertreatment of such patients compromises their prognosis. Moreover, the technical procedure has not been standardized and some aspects have yet to be clarified. For example, it has not been clearly established whether SLNB is indicated in patients with tumors that are large, multicentric, previously biopsied or non-palpable.

Some surgeons use routine SLNB in daily practice, claiming that the false negative rate is close to 0% in centers with sufficient experience and that false negatives are counterbalanced by the greater diagnostic accuracy of SLNB in patients with micrometastases. We believe that the very low rate of false negatives reported by large dedicated centers would be difficult to achieve in small hospitals where breast cancer surgery is only occasionally performed, and that the advantage of detecting more micrometastases is questionable because the biological and prognostic implications of their detection are not really known. The issue of the prognostic impact of false negative cases should therefore be evaluated in the context of randomized clinical trials.

A further aim of our trial is to standardize the procedure for SLNB throughout our region. A multicenter clinical trial is the ideal means to achieve this aim and to ensure effective quality control. Our pilot study allowed us to test and develop appropriate methods for sentinel node identification and histopathological examination. Initially we used technetium 99m-labeled micocolloid albumin. We then switched to nanocolloid albumin (Nanocoll), which is currently the only drug registered for this use in Italy. We initially injected a relatively high dose of tracer (80-100 MBq), but progressively reduced the dose so as to identify the minimum effective dose for intraoperative detection of the sentinel node. In the present trial we use a dose of 30-40 MBq of Nanocoll injected subdermally 18-24 hours before surgery.

In the pilot study intraoperative frozen section of the sentinel node was performed according to the conventional technique, with simple bisection of the node. However, when using this method we found there was an unacceptable rate of discordance between frozen section and definitive histology (14.8%). We therefore modified our approach as described in the methods section, which is easy enough to be used also in small hospitals. The preliminary results of our trial with this approach show a discordance rate of 4.8% (10/208).

Analysis of the characteristics of the primary tumors and sentinel nodes showed that the distribution in the two arms was well balanced (Tables 1 and 2). Only 11/384 cases were T1a, probably because tumors less than 5 mm are usually non-palpable. The sentinel node was found intraoperatively in 93.5% of cases. In 43.7% we found more than one sentinel node: interestingly, the incidence of multiple nodes was significantly higher in the second arm (51.9%) than in the first arm (35.2%).

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Conclusions

The Clinical Institute Mater Domini is a private institution lacking various diagnostic tools (nuclear medicine, surgical pathology), for which it generally needs to seek external support. This problem was overcome by close collaboration between different disciplines. The work reported in this paper is relevant in terms of the number of patients and the quality of the treatment.

THE ROLE OF SENTINEL LYMPH NODE BIOPSY IN PATIENTS WITH STAGE I/II CUTANEOUS MELANOMA. THE CLINICAL EXPERIENCE AT THE NATIONAL CANCER RESEARCH INSTITUTE OF GENOA, ITALY

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Introduction

The sentinel lymph node (SLN) has recently been recognized as one of the most powerful predictors of the outcome of patients with early-stage (I and II) cutaneous melanoma, as it represents an elective site of lymph node metastases. SLN biopsy may play a significant role in the therapeutic planning for early-stage melanoma patients; in fact, the ability to identify patients with clinically occult lymph node metastases could benefit from complete node dissection (to detect the regional basin(s). The second group of 126 patients (54 males and 72 females; mean age, 53 years; range, 19-78 years) was examined between January 1997 and June 2001; cutaneous melanoma was located in the upper extremities (n = 30), lower extremities (n = 51), trunk (n = 36), and head and neck (n = 9). Each patient underwent preoperative lymphoscintigraphy for identification of the lymphatic basin(s) and intraoperative detection of SLN with a gamma probe.

Three different radiopharmaceuticals were used: alubrines (n = 4), lymphoscint (n = 7), and nanocoll (n = 115). 0.2-0.3 mL of tracer, corresponding to 300 mCi of activity, was injected intradermally at four points around the excision scar of the primary melanoma.

Dynamic study of the lymphatic flow was performed by means of sequential imaging. As soon as the pattern of lymphatic distribution was determined and the regional basin(s) identified, a skin marker was placed on the cutaneous projection of the hot spot.

The location of the SLN was confirmed preoperatively by means of a hand-held gamma detection probe, using either Neoprobe 1000™ or 2000™ (Neoprobe Corp, Dublin, OH).

As regards intraoperative mapping, after induction of general anesthesia Patent Blue-V was injected intradermally around the excision scar of the primary melanoma. The gamma detection probe was used prior to skin incision in the lymphatic basin to confirm the location of the hot spot, so that the surgical wound could remain as small as possible.

The skin flap closest to the primary melanoma was carefully dissected from the underlying tissue without disrupting the lymph vessels. The vessels at the basin edge closest to the tumor were then identified and followed to the first blue-stained lymph node (SLN).

The gamma probe was used to confirm the location of the SLN as well as to assist in the dissection whenever no afferent lymph vessel was detectable.

Both in vivo and ex vivo radioactivity counts were recorded, and the SLN was defined as any blue-stained lymph node, or any lymph node with an in vivo radioactive localization index (node/background ratio) greater than 5 and an ex vivo ratio greater than 10. After removal of the SLN both the central bed and the remainder of the lymphatic basin were searched for residual activity, and additional nodes were removed whenever they fitted the activity ratios required to define the SLN. Wide local excision of the biopsy scar of the primary melanoma was performed following removal of all SLNs.

Results

Of the first group of 39 patients three (7.6%) underwent exploratory surgery in more than one nodal basin, and the SLN was identified in 35 patients (89.7%). Eight of these 35 patients (22.8%) were found to have metastatic melanoma cells in their SLNs, and they all underwent SLND of the affected basin. In the second group of 126 patients 17 (13.8%) underwent exploratory surgery in more than one nodal basin. The SLN was detected in all cases by means of the combined technique (Patent Blue-V and RGS).

As regards the assessment of the specific contribution of the two procedures (Patent Blue-V and RGS) to the identification of the SLN, in four of 126 patients (3.2%) the SLN was detected by gamma detection probe only (hot white SLN), and in no patient was the SLN detected by Patent Blue-V only (Table 1). In 36 of 126 patients (28.6%) the SLN contained metastasis: two of 12 pT1 patients (20%), six of 52 pT2 patients (11%), and 11 of 35 pT3

Material and methods

Between July 1993 and March 2001 190 patients with histologically proven cutaneous melanoma (pT1-T4; thickness >0.75 mm) of the extremities, trunk, and head and neck underwent SLN biopsy and SLND, whenever the SLN was histologically positive. Two subsets of patients were distinguished based on the method of detection of the SLN: patent blue-V only or combined with radioguided surgery (RGS). Hundred and sixty-five patients are currently evaluable. The first group of 39 patients was recruited from July 1993 to December 1996 (17 males and 22 females; mean age, 51 years; range, 17-84 years). The location of the primary melanoma was upper extremities (n = 9), lower extremities (n = 15), trunk (n = 14), and head and neck (n = 1). Patients underwent preoperative lymphoscintigraphy whenever the primary lesion was located in ambiguous sites in order to detect the regional basin(s).
patients (31%), and 17 of 27 pT 4 patients (63%). No mortality or major complications related to the procedure were observed.

**Discussion**

In recent years the most relevant technological progress in the field of SLN biopsy has been the introduction of RGS, which is performed with a hand-held gamma probe; use of the hand-held probe has increased the detection rate up to 98-100%. In our experience the use of Patent Blue-V only allowed detection of the SLN in 89.7% of patients (35/39), while the combined use of Patent Blue-V and RGS resulted in a detection rate of 100%. Notably, in four of 126 patients (3.2%) the SLN was detected by RGS only, whereas SLN detection by Patent Blue-V only occurred in none of the patients. This would suggest that the use of the blue dye is not essential for SLN detection because the gamma probe identified all SLNs that were harvested. In the present study, however, the SLN was always identified using both methods because patients were not assigned to a specific method of detection. Certainly, the blue dye and gamma probe techniques are complementary; the probe allows to target the highest area of radioactivity (the skin hot spot) corresponding to the site of the SLN prior to skin incision, resulting in a smaller and more direct biopsy incision. Soon after skin and subcutaneous fat incision, identification of the blue-stained afferent lymph vessel allows to easily direct the probe towards the SLN, thus accelerating SLN detection and reducing tissue plane disruption with a lower risk of wound complications (seroma or wound infection). The gamma probe may also help to differentiate the true SLN from a secondary-echelon node (non-SLN); in fact, the first blue-stained node encountered may actually be a secondary-echelon node that has received the blue dye through an afferent lymph vessel attached in series to the true SLN. This secondary node is a non-SLN, and will not accurately stage the nodal basin. Instead the gamma probe ensures correct identification of the first node directly draining the tumor site, the true SLN, because this node will have the highest radioactivity. Finally, the gamma probe is indispensable in anatomically “difficult” areas, such as the axillary region, because the SLN may be buried deep in fat, close to subcapsular vessels, especially in patients with melanoma on the back or shoulders.

**References**


**INTRAOPERATIVE SENTINEL NODE DETECTION BY AN INNOVATIVE IMAGING PROBE**

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**Abstract**

Intraoperative tumor detection has been used in many applications, and today the sentinel node technique is a widely employed surgical procedure in breast cancer. Different detector systems are employed but several problems have been reported in clinical practice, in particular the difficulty to accurately detect the sentinel node within the axillary soft tissue. The problem is even greater for abdominal and thoracic tumors. We propose an innovative Imaging Probe (IP) able to visualize on a monitor the primary tumor and secondary lesions, if appropriately radiolabeled. The IP can be optimally applied for minimally invasive surgery in breast cancer treatment, and a preliminary experience related to 15 patients and 20 sentinel nodes is reported here. We compared the results obtained with the IP to those obtained with an Anger camera and a traditional scintillation detector, and found them to be very promising. In particular the surgeon’s work is greatly facilitated by direct visual guidance instead of a generic acoustic signal.

**Key words:** intraoperative scintigraphic detection, sentinel node biopsy.
Introduction

The last decade has witnessed important progress in radioisotope diagnostic techniques, and substantial results have been obtained both by adopting new radiotracers and improving new radiation detectors. In particular the intraoperative use of subdermally injected radionuclides can be considered fundamental in the sentinel node biopsy technique for breast carcinoma. The largest devices employed are used to detect single events (pulse mode), adopting a single-channel pulse height analyzer to read radioactivity spots against background or other extraneous events. This type of device indicates the source of radiation by an acoustic signal but such guidance is often considered unsatisfactory by the surgeon; moreover, a learning period including at least 30 procedures is a prerequisite for good clinical results.

Our multidisciplinary team has produced a number of international patents registered for analogous devices. We are currently working on a new multichannel detector for the production of a new analyzer that can provide direct visualization of lesions on a monitor.

In the future it may be possible to use scintillation detectors in the operating room that are as easy to handle and as convenient as traditional devices, with the additional possibility of visualizing the radiation source similar to visualization with an Anger camera. This work shows our preliminary experience aimed at improving the device and procedures.

Methods and study design

The prototype of the Imaging Probe (IP) is equipped with a Hamamatsu R7600-00-C8 (Hamamatsu, Japan) position-sensitive photomultiplier tube (PSPMT) with charge readout electronics. The second series is characterized by several technical modifications aimed at improving the performance and manageability of the device. The latest model has an incorporated probe (intraoperative unit, Figure 1) and is interfaced with a scintillation imager by a control unit board for event processing (external unit). The final images are sent to a high-resolution monitor. The probe weighs about 750 grams and its maximum diameter is 3 cm. It is made sterile by an external transparent plastic cover, similar to those commonly employed for laparoscopic instruments. The prototype used in this study the external unit was a dedicated PC, which was replaced in the operating room by a 500 MHz, Pentium III-powered laptop computer with a high resolution monitor. Acquisition and image processing software was developed with Graphics-Language Lab Windows C++ (National Instruments, USA.). The energy window was operator-selected and centered on the 140 keV +/- 20% peak of 99mTc. The settlement of images was also operator-selected, and a matrix ranging between 32 x 32 and 64 x 64 pixels was adopted in this study. Images appeared on the monitor in multicolor or logarithmic gray scale, initially after a maximum delay of very few seconds and then practically in real time.

In this preliminary study 15 patients with cT1-2N0M0 breast cancer confirmed by cytotological examination of fine-needle biopsy samples were examined with the IP during surgical procedures. A traditional probe (Neo 2000, Neoprobe, USA) was available in case the innovative IP was unable to localize the sentinel node(s). Twenty-four hours before surgery patients were injected with 99mTc Nanocoll (Nycomed-Amersham-Sorin, Saluggia, Italy) in the peritumoral area and ultrasound guide was adopted. Two hours before surgery lymphoscintigraphy was performed with a 40-cm-field-of-view Anger camera (Starcam 4000, GE Mil, USA) and subsequently the IP was used to guide the surgeon to the primary tumor and sentinel lymph node. The results were assessed according to subjective (surgeon’s information) and objective criteria (postoperative control with IP and Neo 2000 to show the presence of possible residual nodes).

Results

The IP detected all lymph nodes shown prior to surgery with the Anger camera. In nine patients there was only one neoplastic node, in five cases two nodes were visualized, and in one patient three distinct adjacent nodes were detected by IP. Histological examination identified five metastases with hematoxylin and eosin and another with cytokeratin immunostaining. Overall, four patients were found to have lymph node metastases (N1). No lymph nodes were identified with the Anger camera that were not visualized by IP and vice versa. Neo 2000 was not necessary in any of the surgical procedures and all postoperative controls with traditional probe (and IP) were negative for residual emission. Figure 2 shows a typical image obtained with the IP.

Discussion

The sentinel node biopsy technique for breast cancer has been extensively validated in phase I and II studies. However, no data from phase III randomized clinical studies are available. It remains controversial whether a histologically negative sentinel node biopsy without further axillary dissection can be considered to be good clinical practice.

Additional problems have yet to be resolved, such as the accuracy of examination of nodes especially during surgery, but can’t be underestimated the fact that somebody treats the argument as “minimally invasive surgery”.

Sentinel node biopsy is easy to perform and provides the surgeon with important supplementary information during surgery.

Figure 1 - Prototype of the intraoperative Imaging Probe. It is interfaced with a scintillation imager by an external control unit board for event processing. A dedicated PC or laptop computer with a high-resolution monitor can be used as external unit.

Figure 2 - The Anger camera image (black and white on the left). The sentinel node in the circle is highlighted by the color image on the right obtained in the operating room with the IP.
In the near future it is likely to become the standard of care in the management of patients with non-invasive breast cancer. Moreover, if we consider the literature of the last decade, it can be expected that the sentinel node procedure will become widely used also in other types of cancer.

Undoubtedly IP has several advantages over the Anger camera and other traditional probes used for sentinel node identification. The Anger camera is the reference for IP’s sensitivity, but the portable device is easier to handle and can actually guide the surgeon’s hand during the operation. It can resolve every problem related to the position of the patient and her breast and arm.

The traditional probe is as easy to handle as IP, but often it is very difficult for the surgeon to get to the exact point of radiation emission with only the guidance of an acoustic signal. Under normal circumstances the surgeon uses mainly his eyes as a guide, and can continue to do so with the IP. As a matter of fact, no learning period is necessary to master the use of the IP, while for the traditional probe experience including at least 30 procedures is a prerequisite for good clinical results.

References

SENTINEL LYMPH NODE ANALYSIS IN SQUAMOUS CARCINOMA OF THE ORAL CAVITY AND OROPHARYNX
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Aims: The aim of our study was to evaluate the usefulness and applicability of sentinel lymph node (SLN) identification in N0 carcinomas of the oral cavity and oropharynx. Study design: We carried out a prospective evaluation of SLN identification in 20 patients with oral cavity or oropharynx carcinomas with no clinical evidence of lymph node metastases. Methods: Peritumoral infiltration with technetium-99-labeled nanocolloid followed by lymphoscintigraphy was carried out approximately 18 hours prior to surgery. A vital dye was injected intraoperatively and the SLN was identified with the aid of a gamma probe. All patients underwent routine neck dissection. Results: While multiple radioactive nodes were generally identified on lymphoscintigraphy, the number of nodes ranging from one to five with variable degrees of uptake, intraoperative gamma probe scanning allowed the identification of a single more radioactive lymph node in 19 of the 20 patients. In only one patient did this method lead to the identification of two equally highly radioactive SLNs, with no uptake in the remaining nodes. All SLNs were ipsilateral to the neoplastic lesion. In 15 cases the SLN was tumor negative and so were the remaining nodes obtained by comprehensive neck dissection. In five cases the SLN was the only lymph node containing micrometastasis among those observed by dissection. There were no instances of node positivity not involving the SLN. Conclusions: Sentinel lymph node identification in ENT surgery may indicate intraoperatively if node metastases are present, thereby avoiding overtreatment in a substantial proportion of patients with NO carcinomas of the oral cavity or oropharynx.

Key words: oral cavity carcinoma, oropharynx carcinoma, sentinel lymph node.

Introduction
The presence of lymph node metastases is the most relevant prognostic factor in head and neck carcinomas. Neck lymph node dissection of all clinically NO patients with head and neck carcinomas has entered routine surgical practice both for prevention and staging purposes; this is due to the reported incidence of lymph node involvement in head and neck cancer ranging from 15% to 60%1.

All neck dissection approaches are associated with significant early and late complications2. Early morbidity is related to surgical bleeding problems and wound healing failure with associated infectious and, more rarely, necrotic events. Late complications include a number or sequelae such as facial and laryngeal edema, sensory deficits in areas supplied by upper cervical branches, marginal nerve paralysis, spinal nerve deficit and scarring with subcutaneous fibrous band formation.

A more accurate and specific identification of lymph node micrometastases might help to avoid overtreatment of approximately 40% of patients with NO oral cavity or oropharyngeal carcinomas and reduce the morbidity associated with surgery. This is potentially achievable by identification of the sentinel lymph node, i.e. the first lymph node draining the area involved by the tumor.

If the value of sentinel lymph node (SLN) analysis in the context of N0 carcinomas of the oral cavity and oropharynx were to be confirmed, node excision could be limited to the SLN in cases where this node is histologically negative. The SLN approach has been successfully employed in breast cancer and cutaneous melanoma3-4.

This study prospectively evaluated this approach over a two-year period (1999-2001) in 20 patients with oral or oropharyngeal cancer undergoing routine surgical management.

Materials and methods
SLN identification was carried out in a group of 20 patients with oral cavity or oropharyngeal carcinomas. Selection criteria included: a) stage T1,2, N0, M0; b) non-palpable lymphadenopathy and no detectable lymph node enlargement on sonography, CT or MR; c) biopsy-proven pathological diagnosis of the primary lesion; d) age between 18 and 65 years. Exclusion criteria included a) multifocal malignancies; b) previous surgery, radiotherapy or burns of the neck region; c) allergic disorders; d) pregnancy.

Patients were enrolled from two different centers participating in the study. Common diagnostic and staging protocols were employed. Lymphoscintigraphy was performed centrally by a single
nuclear medicine specialist. Pathological diagnosis was made according to standard definitions. All patients gave their consent after being thoroughly informed about the aims of the study.

Approximately 18 hours prior to surgery all patients underwent lymphoscintigraphy by injection of technetium-99m-labeled nanocolloidal albumin (mean particle diameter <80 nm) in the normal mucosa at four cardinal points in proximity of the primary lesion. For easily accessible tumors insulin needles were employed while for more deeply located lesions, eg in the retromolar triangle, a 27-gauge spinal needle was used. The total volume of each administration was approximately 0.1 mL with a cumulative volume of <0.4 mL and a total dose of approximately 120 MBq, which is equivalent to a radioactivity of 10-15 MBq at the inoculation sites during surgery. Radiation exposure was thus negligible.

Patients were then placed in the supine position under the gamma camera. Scintigraphic image acquisition was started five minutes after radiotracer administration and generally did not last more than 30 minutes, which is sufficient to trace the radiocolloid in the local lymphatic system. At the end of the scan, ie after both anterior and lateral projections had been acquired, a radioactive pen was used to delineate the patient profile and define the anatomical position of the SLN, which was then marked on the skin to guide the surgical incision. In 10 patients an intradermal peritumoral injection of 1 mL of isosulfan blue, a vital dye with marked tropism for lymphatic tissues, was administered during surgery.

After transcutaneous localization of the SLN an incision of a few centimeters was made following the neck dissection incision lines until the most radioactive SLN was identified, which was excised. In cases where isosulfan blue was used the concordance between the dye and isotope uptake was determined. This was followed by neck dissection according to standard techniques.

The pathologist examined and recorded the SLN separately from the remaining neck dissection lymph nodes. The SLN was measured and cut in 2-mm sections along its greatest diameter. Three-micron-thick coupled histological sections were prepared at 100-micron intervals covering all available tissue and hematoxylin-eosin staining of the first section of each 100-micron interval was performed. In addition, immunohistochemical staining of parallel sections selected by the pathologist was performed with a cocktail of anti-cytokeratin antibodies (AE1, AE3 and PCK26).

Results

SLNs were identified in all cases and there was full agreement between lymphoscintigraphic findings and intraoperative gamma probe detection. Multiple radioactive nodes were generally identified on lymphoscintigraphy, ranging from one to five with variable degrees of uptake. Intraoperative gamma probe scanning allowed the identification of a single more radioactive lymph node in 19 of the 20 patients. In only one patient did this method lead to the identification of two equally highly radioactive SLNs, with no uptake in the remaining nodes. In all cases the SLN was located ipsilateral to the tumor lesion.

Less encouraging results compared to previous reports were obtained with vital dye studies, which were informative in only six of the 10 patients studied; in these six patients, however, the stained lymph node was also the one with radioactive uptake detected by gamma probe.

In 15 cases the SLN was negative, like the remaining nodes obtained by comprehensive neck dissection. In five cases the SLN was the only node containing micrometastasis among those obtained by dissection. There were no instances of node positivity not involving the SLN.

Discussion

SLN identification is simple and reproducible; it has been demonstrated to be quite reliable and a dependable predictor of tumor cell dissemination in breast cancer and melanoma of several sites including the head and neck. The routine clinical use of SLN identification and assessment in patients with oral cavity carcinomas with no evidence of tumor spread could avoid overtreatment and its complications. In fact, approximately 40% of N0 patients are at risk of significant complications resulting from prophylactic neck dissection.

In five cases of the present series tumor cells were detected only in SLNs and we observed no instances of multiple node positivity which did not include sentinel nodes, suggesting that lymphoscintigraphic findings parallel micrometastatic spread. A tumor-positive SLN on microscopic examination is a reliable predictor of local lymphatic dissemination. Our study strongly supports the usefulness of this technique in oncological ENT surgery. Many studies are currently ongoing that will elucidate whether SLN analysis, rather than being considered an experimental procedure, should be introduced into routine surgical practice.

Conclusions

Sentinel lymph node analysis may allow intraoperative assessment of the presence of metastatic spread in ENT malignancies. As in other malignancies, the SLN is excised and sent to the pathologist, who divides it into two equal parts at the level of the hilum; one half undergoes immediate intraoperative examination. In this way patients with no evidence of SLN metastasis could be spared invasive neck dissection. The remaining portion of the SLN is studied with standard staining as well as anticytokeratin immunohistochemistry.

References


NEW FRONTIERS OF NUCLEAR MEDICINE

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In recent years, nuclear medicine has contributed significantly to the diagnosis, staging, follow-up, and evaluation of therapeutic response of cancer patients. One of the most prominent tools of nuclear medicine whose clinical applications are continuously increasing is positron-emission tomography (PET) imaging. The most important current application of PET is the semiquantitative measurement of tumor metabolism. In fact, PET images of glucose uptake may differentiate tumor grades based on the intensity of FDG uptake. The uptake of FDG reflects the metabolic rate of the tumor, which is usually higher than that of the surrounding normal tissue1. PET has an established clinical role in tumors such as lung cancer, lymphoma, and brain tumors. Clinical studies are being performed on colorectal carcinoma, melanoma, breast cancer, pancreatic carcinoma, musculoskeletal sarcoma, and head and neck tumors. PET has proved useful in the differential diagnosis of solid pulmonary nodules, which can be identified— with reliable accuracy if larger than 1 cm—as malignant or benign; in the latter case transthoracic or transbronchial biopsy is unnecessary. However, the specificity is limited because inflammatory lesions may cause a PET image to be falsely positive for malignancy, and the presence of FDG uptake in a lung nodule therefore requires histological diagnosis2. PET is also useful in differentiating pancreatic carcinoma from mass-forming pancreatic and in the diagnosis of breast cancer in patients with dense breasts or implants, which render mammography or biopsy poorly reliable3. PET can be used in the staging of mediastinal lymph nodes in lung cancer4 and of regional lymph nodes and distant metastases in melanoma, while in Hodgkin’s and non-Hodgkin’s lymphomas it may be useful as a baseline for treatment follow-up5. In ovarian, head and neck and pancreatic carcinomas PET may provide sensitive whole-body screening when tumors are at an advanced stage3. PET can also be applied in the differentiation of scar tissue from residual or recurrent disease and is able to distinguish between radiation necrosis and tumor recurrence in the brain6. A similar differentiation seems to be of use also in lung and head and neck tumors. In colorectal cancer PET can be of help in the detection of recurrences in patients with high CEA levels and, when pelvic masses remain indeterminate on CT, in distinguishing between scar tissue and tumor recurrence7. PET has proved to be useful in monitoring therapy in Hodgkin’s and non-Hodgkin’s lymphomas, where identification of persistent disease after first-line treatment imposes the use of more aggressive regimens often including high-dose programs followed by bone marrow transplantation8. Several studies have shown that PET can detect axillary lymph node metastases with relatively high sensitivity and specificity and with a negative predictive value of 95%. However, a limitation of this approach is that 5% of women with lymph node micrometastases not detected by PET will be understaged. Therefore, for staging of early breast carcinoma, identification and sampling of the sentinel lymph node may be the procedure of choice9. In fact, lymphatic mapping with sentinel node biopsy is rapidly becoming the standard procedure for assessing axillary lymph node status and obviating axillary lymph node dissection in patients with node-negative breast cancer10,11. However, many technical issues influence the results. For instance, which should be the acceptable rate of false negatives to avoid axillary node dissection on a routine basis and which tests are required to obtain pathological evidence of lymph node involvement? Therefore, specific guidelines and documentation of extensive experience and a low false-negative rate for surgeons and hospital teams carrying out the procedure are needed for its application on a large scale9.

The knowledge acquired in recent years of molecular mechanisms can be merged with nuclear medicine, leading to the development of a variety of new molecular imaging probes such as peptides, hormones, new monoclonal antibodies, enzymes, nucleotides and receptor ligands. All these new probes and techniques can be exploited to image a variety of biological processes such as apoptosis, angiogenesis and transgene expression12. Apoptosis appears to be an essential part of the pathogenesis of a variety of diseases. Imaging of apoptosis would be a useful aid in the development of new drugs and in monitoring the effectiveness of therapy. A target that can be used for this purpose is phosphatidylserine; this phospholipid is normally present in the internal layer of the cell membrane but is rapidly exposed by apoptotic cells. The ligand used is annexin V, a protein with high affinity for phosphatidylserine that can be labeled with 99mTc. It has been demonstrated that this radiopharmaceutical binds to cells undergoing apoptosis in vitro and permits imaging of the process in animal models13. Thus far apoptosis imaging with 99mTc-annexin V has been successful in transplant rejection and Fas-induced hepatic apoptosis. There are many other systems where this approach should be tested, such as antitumor chemotherapy, ischemic and hypoxic tissue injury and induced autoimmune disease. Because the agent is a physiological protein, it may be suitable for human testing in the near future14.

Angiogenic and antivascular agents represent a new approach to the treatment of cancer. Imaging techniques such as CT, MRI, ultrasound and PET that are ordinarily used to document tumor masses may be adapted to measure vascular parameters such as blood flow, blood volume, permeability, microvessel density, and tumor metabolism15. In fact, the small size of microvessels precludes direct visualization by conventional angiography. Moreover, patients enrolled in cancer trials often have advanced disease, with a heavy tumor burden. Such tumors will possess an extensive vascular supply. Angiogenesis imaging systems therefore must be able to accurately quantify small changes against a potentially large signal background. Furthermore, antiangiogenic therapy is envisioned to require lifelong treatment, so a non-invasive, cost-effective technique would be highly desirable16. The clinical monitoring of antiangiogenic therapy requires an imaging modality that is capable of detecting tumor vascularization and its changes with high sensitivity and specificity. These requirements can be met by PET imaging, which is able to detect the diminished blood flow and subsequent decreased tumor metabolism caused by antiangiogenic agents17. Future approaches for angiogenesis imaging are likely to exploit the molecular features of new blood vessel growth with novel imaging targets such as cell surface integrins, endothelial apoptosis, or angiopoietins18.

Gene therapy is one of the most promising new treatments for cancer. Several approaches use retroviruses to transfect cancerous cells in vitro and permit imag-
A SIMPLIFIED PROCEDURE FOR CONTINUOUS INTRAOPERATIVE EXTERNAL MONITORING OF SYSTEMIC LEAKAGE DURING ISOLATED LIMB PERFUSION

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Abstract

Aims: Isolated limb perfusion (ILP) with high doses of an alkylating agent alone or in combination with tumor necrosis factor (TNF) in hyperthermic conditions (HAP) has been proposed for the treatment of locoregional tumors. A critical step in ILP/HAP is accurate monitoring of systemic leakage to prevent the toxic effects of chemotherapy, and in particular of TNF. Ten percent systemic leakage from the perfusion circuit is considered the maximum acceptable leakage. In this study we report our experience on a new leakage monitoring system. Materials and methods: This new simplified procedure is based on the use of ⁹⁹ᵐTc-labeled soluble human serum albumin (HSA) and a hand-held gamma probe as detector. The procedure consists of the following steps: 1) A standardized ⁹⁹ᵐTc-HSA dose of 0.5 MBq/kg body weight is injected into the perfusion circuit before chemotherapy/TNF perfusion, and a hand-held gamma probe (IGP) is placed over the precordial area in a zone that was marked on the skin during a simulation test; 2) 48-72 hours before ILP/HAP a complete simulation test is performed with a ⁹⁹ᵐTc-HSA dose corresponding to 10% of the total dose calculated for the patient’s body weight; 3) during the simulation test the maximum count-rate zone on the precordial area is detected by IGP and marked on the patient’s skin; 4) a 60-min curve of effective ⁹⁹ᵐTc-HSA radioactivity decay (physical and biological) is calculated and fitted; 5) to compare external counting with the effective circulating radioactivity, patient blood samples and circuit blood samples are taken every five minutes during ILP/HAP and measured by a laboratory gamma counter and very convenient thanks to the favorable characteristics of IGP. Theplaced in the operating room. Results: External counting with a hand-held gamma probe was easy to perform time/activity curves obtained during simulation tests showed a regular and constant effective decay with a mean decay rate of 30% at 60 minutes compared to baseline values. The external measurements obtained by IGP proved to be well correlated with blood samples measured in vitro by a laboratory gamma counter. The results of this procedure, in particular the data of the simulation test for each patient, allowed us to correct the limit of 10% maximum leakage during ILP/HAP in accordance with the time/activity curve. Conclusions: Although ⁹⁹ᵐTc-HSA has some unfavorable characteristics, it offers many advantages over ¹³¹I-HSA. The procedure proposed by us, which was based on the use of an IGP and ⁹⁹ᵐTc-HAS at a standardized dose of 0.5 MBq/kg body weight and on an individual simulation test for each patient performed 48 hours before ILP/HAP, proved to be simple and accurate in monitoring systemic leakage during ILP/HAP anticancer therapy.

Key words: hand-held gamma probe, hyperthermic antiblastic perfusion, isolated limb perfusion, leakage monitoring. ⁹⁹ᵐTc human soluble albumin.

References


thymidine kinase/ganciclovir (HSVtk/gcv) system. PET imaging of ganciclovir labeled with ¹³¹I and used as a marker substrate whose level of accumulation is sensitive to HSVtk enzyme levels was performed in animal studies.¹²,¹³ By using the PET scanner to pinpoint the location of the genes, researchers will be able to monitor the action of the gene therapy soon after it has been administered to a patient. Doing so will allow them to establish rapidly whether the therapy attacks cancer cells or travels elsewhere in the body, potentially exposing the patient to serious side effects.¹³

These new imaging modalities, combined with optimized trial design agents, will create a robust platform for a vast variety of future nuclear medicine applications in standard practice.
Introduction

Isolated limb perfusion (ILP) therapy was first proposed for the treatment of cutaneous melanoma in 1958. ILP therapy with an alkylating agent alone or combined with hyperthermic antitiblastic perfusion (HAP) at high doses in patients with melanoma, osteogenic sarcoma and other less frequent sarcomas induces complete remission of local disease in more than 50% of patients. An efficient ILP/HAP system allows to regionally deliver elevated dose levels of chemotherapeutic compounds without any systemic toxicity. In an HAP system the addition of tumor necrosis factor-alfa (TNF) at doses 10-fold higher than those tolerated during systemic administration increases the complete remission rate for melanoma and soft tissue sarcoma. The use of TNF for systemic therapy has been limited by its severe toxicity, and the maximum tolerated dose of TNF for systemic administration is lower than that necessary to obtain antitumor effects.

For this reason the use of TNF has to be combined with an accurate ILP/HAP procedure. Monitoring of leakage into the systemic circulation is mandatory during ILP in order to keep TNF and chemotherapeutic agents within acceptable serum levels. For this purpose different techniques have been proposed, which generally combine radioactively labeled human serum albumin (HSA) with blood sample measurement or external scintillation probe detection. The most widely applied technique is based on the use of 131I HSA and precordial counting with an external scintillation probe, first proposed by Stehlin et al. in 1961. This method was improved in 1995 by Barret et al. after the introduction of TNF in ILP/HAP therapy, which necessitated control and real-time monitoring of TNF levels in systemic perfusion in view of the toxic effects of TNF. This technique is accurate and allows real-time monitoring of perfusate leaks; however, it has a number of disadvantages, including the use of 131I HSA; in many countries this radiopharmaceutical is not registered for human use, and it is associated with a number of problems of handling and waste risk. Moreover, the technique is based on the use of an external scintillation detector, which is an obsolete instrument and unmanageable in the operating room. The aim of this study was to design a simplified and effective procedure based on the use of 99mTc-HSA but reducing its unfavorable characteristics by appropriate measures, combined with an intraoperative gamma probe (IGP) for real-time leakage monitoring during ILP.

Materials and methods

Patients

Forty-six consecutive patients (24 women, 22 men; median age, 53 years; range, 19-73) with melanoma or sarcoma of the extremities underwent ILP/HAP combined with TNF. All patients were treated after appropriate informed consent had been obtained. The ILP/HAP procedures were performed using a recently described standardized technique.

Monitoring methods

As tracer agent we chose a commercial preparation of human serum albumin (HSA), (Technesca HSA, Mallinckrodt, Petten, Holland), labeled with 99m-technetium (99mTc) according to the package instructions. 99mTc-HSA was injected into the perfusion circuit 24-72 hours before the ILP/HAP procedure the patient was studied with a 10% dose of the same tracer (0.05 MBq/kg/bw). The tracer was injected intravenously and the patient was followed for one hour with a hand-held gamma probe placed on the precordial area. This simulation test was useful to obtain a 60-min curve of the effective 99mTc-HSA decay and to mark the maximum count-rate zone on the patient’s skin over the heart. The precordial skin mark was used to place the gamma probe correctly during the ILP/HAP procedure.

Results

The simulation test performed in each patient before treatment with ILP/HAP showed a slow and continuous effective radioactivity decay with a mean decay rate of 30% 60 minutes after tracer dose injection. This result was used in the operating room to correct the effective systemic leakage from the perfusion circuit on line. In fact, continuous radioactivity recording enabled us to depict for each patient an individual 60-min time/activity curve of effective decay. This curve, recorded on paper or directly on a portable computer connected to the IGP, was used in the operating room during ILP/HAP to monitor step by step the effective maximum limit of 10% leakage from the perfusion circuit with a scale of 1% steps. A second advantage of the simulation test was that it enabled us to mark the maximum count-rate precordial area on the patient’s skin, thus allowing easy and correct placement of the IGP during the ILP/HAP procedure. Leak values obtained from in vivo monitoring measured by IGP placed on the precordial area correlated significantly with values obtained from systemic blood samples measured every five minutes by means of a laboratory gamma counter placed in the operating room.

Discussion

The use of TNF combined with alkylating agents in ILP/HAP warrants accurate and continuous monitoring of possible leakage from the perfusion circuit to the systemic circulation so as to limit the toxic effects of TNF. Leakage monitoring is usually done with a radioactive tracer and an external counter. The most widely applied technique, which was first proposed by Stehlin and subsequently improved by Barker, uses 131I HSA and an external gamma probe. In this study we propose a simplified technique based on the use of 99mTc-HSA and an IGP to obviate the disadvantages of 131I HSA, such as its long half-life and the risk of radiation exposure for patients and surgical staff, as well as the unfavorable features of an external gamma probe such as poor manageability and obsolescence. Furthermore, in order to reduce the few unfavorable characteristics of 99mTc-HSA such as physical and biological decay, we propose an individual simulation test for each patient carried out 48 hours before ILP/HAP. The results of this study demonstrate that the procedure is simple and easy to perform. The use of 99mTc-HSA is convenient because 1) this radiopharmaceutical has been registered for use in humans; 2) it can be prepared and calibrated on site; 3) it has a low risk of waste; 4) it presents a low radiation risk to patients and surgical staff. The IGP is widely used in many surgical departments because of its application in sentinel node biopsy, it is a handy tool and highly effective in radioactivity measurement. Moreover, the simulation test we proposed in combination with standardization of 99mTc-HSA was able to overcome the unfavorable characteristics of this tracer and provided an accurate time/activity
curve of effective decay applicable to leakage monitoring. The accuracy of our procedure was confirmed by means of patient blood sample and perfusion circuit sample measurements. In conclusion, in our experience the simplified procedure proposed seems to be easy, safe and very accurate in monitoring systemic leakage during ILP/HAP cancer therapy.

References
recurrent HPT after first surgery performed at another clinical center and seven patients had undergone previous thyroid surgery. The IGP technique included the following steps: a) in the operating room a low dose (37 MBq) of 99mTc-MIBI was injected during anesthesia induction; b) subsequently, the patient’s neck was scanned with the probe to localize the cutaneous projection of the enlarged parathyroid gland; c) in patients undergoing MIRS the PA was intraoperatively detected with the probe and removed through a small (2-2.5 cm) incision in the skin; d) radioactivity was measured on the enlarged parathyroid gland both in vivo and ex vivo, and on the thyroid, background and parathyroid bed after PA removal. In patients with concomitant nodular goiter the radioactivity was also measured on thyroid nodules. For the IGP technique we used a commercially available probe with an 11-mm diameter (Pol.hi.tech, Italy). Quick parathyroid hormone (QPTH) was measured intraoperatively in all cases to confirm the radicality of parathyroidectomy.

Results
Surgical and pathological findings were consistent with a single PA in 120 patients (93.7%), parathyroid carcinoma in two (1.5%), and MGD in six (4.7%). MIRS was successfully performed in 94 of the 97 patients (96.9%) in whom this approach was planned (group 1). The IGP technique proved particularly useful in detecting PAs located at ectopic sites (six in the upper mediastinum and two at the carotid bifurcation) and deep in the neck (11 in the paratracheal/parasphageal space). MIRS was also successfully performed in the 23 patients who had previously undergone parathyroid or thyroid surgery. The mean operative time of MIRS was 36 min (range, 15-58 mins). In the remaining three patients (3.1%) of group 1 conversion to BNE was required because a parathyroid carcinoma (two cases) or MGD (one case) were diagnosed during surgery. It is worth noting that in the patient affected by MGD, in contrast to the other patients of group 1, QPTH remained elevated after the removal of the preoperatively visualized enlarged parathyroid gland, suggesting the persistence of occult hyperfunctioning parathyroid tissue; another contralateral enlarged parathyroid gland was found at BNE and final histological examination was consistent with double adenoma. In the patients in whom a BNE had been planned (group 2), the IGP helped the surgeon to localize a supernumerary thymic parathyroid gland in a case of MGD, and a deep or ectopic PA in three cases with concomitant nodular goiter (at the right carotid bifurcation in one case, in the right paratracheal space in one, and in the retrotracheal space in one). However, it must be underlined that it was difficult for the surgeon to differentiate with the probe radioactivity of PAs from that of thyroid nodule(s) in some other patients with nodular goiter, particularly in cases where the PA was located close to a MIBI-hot thyroid nodule. In these patients careful evaluation of the preoperative scintigraphic findings was very important to avoid false-positive results at radioguided surgery.

Nine cases of transient hypocalcemia were observed following surgery. No laryngeal nerve palsy or persistent or recurrent HPT was recorded after a median follow-up of 11 months (range, 2-24 months). Two cases of permanent hypoparathyroidism were observed after subtotal parathyroidectomy for glandular hyperplasia.

Discussion
MIRS is the most recent surgical technique proposed to perform a selective parathyroidectomy in primary HPT patients with a high likelihood of being affected by a solitary PA. The first promising results with this approach were reported by Norman and Chhe-da in 1997. Norman’s protocol consists of the following steps: 1) the patient is injected with 99mTc-MIBI (740 MBq) in the nuclear medicine department; 2) preoperative imaging is obtained with a dual-phase scintigraphic technique; 3) then the patient is operated on using the IGP technique. The main advantage of this protocol is that nuclear imaging and surgery take place on the same day. Our protocol presents various differences: 1) preoperative imaging is performed on a different day than surgery; 2) scintigraphy is performed using a double-tracer technique; 3) a very low 99mTc-MIBI dose (37 MBq) is injected to the patient in the operating room immediately before the start of surgery. We use a two-day protocol because it allows better planning of the extension of surgery. In fact, in our country the prevalence of nodular goiter concurrent with primary HPT is rather high, up to 30% of cases; in these patients, especially in those in whom thyroid nodule(s) are located in the thyroid lobe contralateral to the PA, MIRS is preferably avoided and partial thyroidectomy is generally performed together with parathyroidectomy. Furthermore, it has been reported that thyroid nodules can be 99mTc-MIBI avid; consequently, they can mimic parathyroid lesions, leading to false-positive scintigraphic results when the dual-phase scintigraphic technique is used. For this reason we prefer an imaging protocol based on double-tracer scintigraphy combined with neck ultrasonography in order to preoperatively diagnose both thyroid and parathyroid lesions: in this way only HPT patients with a normal thyroid gland can be selected for MIRS. As far as the IGP protocol is concerned, the injection of a very low 99mTc-MIBI dose in the operating room immediately before surgery has two advantages: 1) radiation exposure of surgeons and operating room personnel is minimal, and 2) potential false-negative results related to PAs with a fast MIBI washout can be avoided. In the present study MIRS was successfully performed in 94 of the 97 patients (96.9%) in whom this approach was planned on the basis of preoperative scintigraphic and ultrasound evaluation. Conversion to BNE was required in only three patients, two with parathyroid carcinoma and one with MGD diagnosed intraoperatively. Importantly, in cases of MGD intraoperative measurement of QPTH played a critical role in determining the conversion to BNE. In our series the IGP technique allowed us to perform MIRS in 16 patients with persistent or recurrent HPT after primary surgery and in seven patients who had undergone previous thyroid surgery, thereby minimizing the extension of reoperation and related complications. It is difficult to define a clear role of radioguided surgery in HPT patients with coexisting nodular goiter. In our experience the IGP technique helped the surgeon to localize two PAs located deep in the neck and one ectopic PA at the carotid bifurcation in patients with nodular goiter. However, since thyroid nodules are often 99mTc-MIBI avid, they may mimic parathyroid lesions on IGP images, thus causing false-positive results. In these cases preoperative imaging with double-tracer scintigraphy (including scintigraphic evaluation of the thyroid) and ultrasound are very important so as to avoid misdiagnosis and unnecessary neck surgery. On the basis of the present data it can be concluded that: a) in primary HPT patients with a high likelihood (based on scintigraphic and ultrasound images) of being affected by a single PA and with a normal thyroid gland, the IGP technique is useful in MIRS; b) a 99mTc-MIBI dose as low as 37 MBq appears to be adequate to perform MIRS; c) the measurement of QPTH is strongly recommended in HPT patients selected for MIRS to confirm complete removal of hyperfunctioning parathyroid tissue; d) MIRS can be useful also in HPT patients who previously underwent parathyroid or thyroid surgery to limit surgical trauma at reoperation and to minimize the related risk of complications; e) in the presence of nodular goiter and 99mTc-MIBI-avid nodules, careful evaluation of the preoperative scintigraphic images is mandatory to avoid possible false-positive results at radioguided surgery: in such patients the IGP technique can be helpful when PAs are located at ectopic sites or deep in the neck.

References
ERRATA CORRIGE

In i supplementi di Tumori (vol 1, No 2, March-April 2002), Symposium on gastrointestinal, liver and pancreatic cancer, page S97 (abstract 146) and page S110, please read S Spirch instead of S Saverio, as erroneously printed.