Radioisotope-guided surgical techniques for the treatment of early breast cancer

Theses of PhD dissertation

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INTRODUCTION

The adoption of radioisotopes during surgery is more than 50 years old (1949). In the early times domestically produced gamma detectors were used intraoperatively. This technique can have owed its development to running gamma-probes to the trade, and to working-up the method of sentinel lymph node biopsy and of direct radioisotope localization of non-palpable lesions.

Recently and fortunately breast cancers have been detected in earlier and earlier clinical stage. Many of these early detected breast cancers proves to be histologically node negative. Previously axillary lymph node dissection was routinely performed for staging and for therapeutic purposes, but this procedure has had significant morbidity, and has also had an adverse effect on the patients’ quality of life. The demand on developing less invasive staging procedures has been emerged. The so called sampling techniques have never been widely spread into the clinical practice because these are rather random than targeted biopsy methods.

The sentinel lymph node concept was developed by Cabanas RM in 1977, who used this for patients with penile cancer. The concept of the sentinel lymph node means that the lymphatic drainage of cancers is not a random process. The sentinel lymph node is the functionally first lymph node of the tumor or the tumor bearing organ. This lymph node can be identified and removed by different methods (dye, radioisotope or both) during surgery. This lymph node most likely and accurately predicts the metastases free status of the other lymph nodes in the same nodal region. In the literature sentinel lymph node biopsy for breast cancer was
published first by Krag DN in 1993. The technique and the indications of sentinel lymph node biopsy, and the method of the pathological evaluation of the sentinel lymph nodes have not yet been defined. Further questions are: 1) can completion axillary lymphadenectomy safely be abandoned in patients with negative sentinel lymph node, 2) what is the optimal treatment of the axilla (if it is even essential!) after positive sentinel lymph node biopsy (surgery vs. radiotherapy)?

After the introduction of organized mammographic screening programs the absolute number and the rate of non-palpable breast lesions have been significantly increased. These lesions should be marked for the surgeon before operation. Various techniques have already been used (marking on the skin surface; marking with dye; marking with stiff and straight needle; marking with hooked-wire; intraoperative ultrasound). These methods however have significant drawbacks, and cause inconveniences and stress for the patients. The radioguided localization technique of non-palpable breast lesions was introduced by Luini A in 1998. The method has since been used for simultaneous sentinel lymph node biopsy.
AIMS AND METHODS

The aim of my work was to investigate the radioisotope-guided surgical techniques for the treatment of different malignancies (breast cancer, malignant melanoma, gastrointestinal cancers). In the dissertation only breast cancer related questions have been discussed. The study can be divided into 3 phases:

Phase 1: Technical feasibility and accuracy studies (1\textsuperscript{st} to 6\textsuperscript{th} points).
Phase 2: Prospective observational clinical investigation (7\textsuperscript{th} point).
Phase 3: Prospective randomized clinical trial (8\textsuperscript{th} point).

1 (Technical study)

In this study the technical feasibility, sensitivity and accuracy of the dual agent guided sentinel lymph node biopsy with preoperative lymphoscintigraphy for staging the axilla has been investigated. The effects of learning curve, different particle size colloids, different injection sites, the characteristics of the primary tumor and the time of operation for the sensitivity and accuracy of the method have been examined. We aimed to work-up an easily reproducible and unifiable technique which is also safe from radiation protection points of view.

2 (Pathological study)

The effect of different histological work-up of the sentinel lymph nodes for the sensitivity of the method has been examined in this study. The feasibility and accuracy of a molecular biological technique (RT-PCR) have also been investigated for detecting metastases in the sentinel
lymph nodes. The sensitivity of 4 potential surgical-pathological axillary staging procedure has been compared with each other.

3 (Radioguided Occult Lesion Localization (ROLL) study)

In this study the technical feasibility of the radioguided non-palpable breast lesion localization method has been investigated for excising occult breast cancer. The possibilities of performing simultaneous sentinel lymph node biopsy and of using this technique for multifocal breast cancer have also been examined.

4 (Ductal carcinoma in situ study)

The clinical role of sentinel lymph node biopsy for ductal carcinoma in situ has been studied in this part. The risk of sentinel lymph node metastasis has been determined as a function of different clinical and pathological characteristics.

5 (Neoadjuvant chemotherapy study)

The aim of this part of the dissertation was to investigate the technical feasibility, the accuracy and the clinical role of sentinel lymph node biopsy after neoadjuvant chemotherapy.

6 (Negative axillary lymphoscintigraphy study)

The value of negative axillary lymphoscintigraphy for prediciting the histological axillary lymph node status has been examined in this study as a function of 2 different radiocolloid administration sites (subareolar and intratumoral) used in our own practice.
7 (Follow-up study)

Routine completion axillary lymph node dissection has been omitted for sentinel lymph node negative patients after the favourable international and own results and after the statement of the 1st National Consensus Conference on the Treatment of Breast Cancer (Eger, 1999) at our Institute in March 2000. After this time completion axillary blockdissection has been performed only on sentinel lymph node positive patients, and patients with negative sentinel lymph nodes have only been observed for the axilla. In this follow-up study it has been investigated whether further treatment of the axilla (completion axillary lymphadenectomy or radiotherapy) can safely been abandoned for patients with negative sentinel lymph node.

8 (Prospective randomized study)

In this prospective randomized clinical trial we aimed to define the optimal treatment of the axilla (completion blockdissection vs. radiotherapy) for patients with positive sentinel lymph node. The trial was activated in August 2002, and the recruitement of patients is now favourably in progress. I will not mention this study later in the dissertation, I mentioned this study only for the aim at completeness.
RESULTS AND CONCLUSIONS

Out of the radioguided surgical techniques sentinel lymph node biopsy has proved to be feasible in our practice for staging malignant melanoma, breast cancer, anal cancer, gastrointestinal-, lung-, thyroid- and testicular tumors. Direct occult tumor localization with radioisotopes has been used successfully for the surgical treatment of non-palpable breast and soft tissue lesions (for soft tissue lesions especially for local recurrences).

Feasibility of course does not mean that these techniques also have clinical significance. Our investigations however has proved the clinical significance of sentinel lymph node biopsy for the treatment of malignant melanoma, breast cancer and anal malignancies. Radioisotope-guided direct tumor localization has also proved to be clinically significant for the surgical management of all kinds of non-palpable lesions.

1 (Technical study)

In this comparative study the dual agent guided sentinel lymph node biopsy with preoperative lymphoscintigraphy using the subareolar injection site, large particle size radiocolloid in small volume and in small activity, and the 2 days procedure has been feasible and highly accurate for the histological axillary nodal staging of breast cancer patients. This technique is easy to learn, easily reproducible and is also favourable of organization and radiation protection points of view.
2 (Pathological study)

Serial sectioning and immunohistochemical examination of the sentinel lymph nodes significantly has improved the sensitivity of the technique. The clinical significance of the detected micrometastases has not yet been determined therefore we do not recommend to perform immunohistochemical examination routinely on the sentinel lymph nodes but we propose to do serial sectioning. The role of the molecular biological (RT-PCR) examination of the sentinel lymph nodes has also not yet known therefore this is recommended only within the scope of prospective studies.

3 (ROLL study)

Radioguided localization of non-palpable breast lesions is one of the most effective (also from the view of reducing costs) and least unpleasant method for the excision of occult breast cancer which also allows performing simultaneous sentinel lymph node biopsy. The technique is also feasible for multifocal breast lesions which was first published in the literature by us.

4 (Ductal carcinoma in situ study)

Performing sentinel lymph node biopsy routinely for ductal carcinoma in situ is not indicated because the lymph node positive and regional recurrence rates are very low. On the basis of our experiences sentinel lymph node biopsy for ductal in situ breast cancer is absolutely indicated only for patients undergoing mastectomy. In other cases we recommend to divide the operation into 2 parts.
5 (Neoadjuvant chemotherapy study)

Sentinel lymph node biopsy is feasible but not so accurate after neoadjuvant chemotherapy by the international experiences. Results show significant dispersion maybe due to the different indications for neoadjuvant chemotherapy. Sentinel lymph node biopsy after neoadjuvant chemotherapy used routinely by us predicts the histological lymph node status accurately but the identification rate is very low so the clinical significance of using this technique routinely in our practice is highly questionable.

6 (Negative axillary lymphoscintigraphy study)

The role of negative axillary lymphoscintigraphy is different using various injection sites for the radiocolloid. Negative axillary lymphoscintigraphy most likely predicts positive axillary lymph nodes after subareolar tracer administration. This is not true for the intratumoral radiocolloid injection technique. We do not have experiences using other injection sites.

We perform axillary lymph node dissection routinely after negative axillary lymphoscintigraphy if the tracer was injected subareolarly. After intratumoral administration of the radiocolloid and negative axillary lymphoscintigraphy to divide the operation into 2 parts is recommended.

7 (Follow-up study)

On the basis of the international and our own experiences irrespective of the relatively short follow-up periods completion axillary
lymph node dissection can safely be omitted for patients with negative sentinel lymph nodes. The rate of axillary recurrences is very low, the sensitivity of nodal staging improves, and the procedure has a very low morbidity rate, so the patients’ quality of life improves significantly.
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LIST OF PUBLICATIONS

Publications in the theme of the dissertation


*Publications out of the theme of the dissertation*


Books and book chapters


Intraoperatív izotópdiagnosztika a daganatsebészetben Szerk.: Köves I, Péley G