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Current status of sentinel lymph node dissection in breast cancer

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Sentinel lymph node dissection (SLND) is being used as an alternative to routine axillary lymph node dissection in the management of clinically node-negative women with breast cancer. In 1991, we began to investigate SLND by injecting a vital blue dye, lymphazurin 1%, into the peritumoral tissue of patients with primary breast cancer undergoing axillary dissection (ALND). Three years later we reported our experience with 174 SLNDs in women who underwent concomitant completion ALNDs. This study was a feasibility trial in which all women, regardless of tumor size or nodal status, were injected with blue dye to determine if we could identify axillary sentinel nodes. Even in this preliminary study, the procedure appeared highly effective, predictive of axillary status in over 95% of the cases. In 1995, we evaluated 162 patients who underwent successful SLND followed by completion ALND and compared them with 134 patients who underwent routine ALND alone. In these cases the sentinel node was evaluated with H&E as well as immunohistochemistry chemical staining, whereas non-sentinel nodes in the ALND were evaluated with H&E alone. We detected a significant higher incidence of axillary metastases in the SLND group than in the ALND group (42 versus 28%, $P < 05$). This was due primarily to the detection of more micrometastases. We then examined all non-sentinel nodes in patients whose sentinel node was negative by immunohistochemistry as well as H&E. We found only one involved lymph node in over 1087 non-sentinel lymph nodes, confirming the hypothesis that the sentinel lymph node is the first lymph node to harbor metastases when they are present. Other investigators around the world have confirmed the sentinel node hypothesis using either vital dyes or radiosotope. Each procedure has advantages, and each is equally effective in experienced hands. For those with experience in the technique, lymph node dissection may not be necessary for women whose sentinel node is tumor-free.

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Upper GI tract – Can extensive lymphadenectomy be avoided?

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Lymphnode (LN) dissection may have a diagnostic or a curative impact in surgical resection of primary upper GI tract tumors like cancers of the esophagus (ESO), stomach (GAS), pancreas (PAN), gallbladder (GAL), proximal two-thirds of the choledochus (CHOL), distal choledochus/duodenum/papilla (PERIAMP) or the liver (HEP). Regional fields/lymph LN stations are usually included without extending the radicality but the time of primary tumor resection. Extensive lymphnode clearance may have a curative aspect in GAS, PAN, GAL, CHOL and PERIAMP (proven e.g. in GAS). Ultraradical LN dissections e.g. with splenectomy/left pancreatectomy in GAS or LN clearance left to the superior mesenteric artery in PAN are of no benefit, increase morbidity and should be avoided. Diagnostic dissections should be extensive only if morbidity is not increased and if all lymphnode stations are registered. Extensive lymphnode dissections in case of macroscopical lymphnode metastases (proven in frozen sections) should be included into primary tumor surgery only if R0 LN clearance is possible. In case of HEP with lymphnode metastases, primary tumor removal and thus – lymphnode dissection is not indicated.

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Lymph node surgery in colorectal cancer – Today and tomorrow

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The rationale for lymph node surgery in colorectal cancer today is relying upon the current interpretation of the order of lymphogenic spread from paracolic to intermediate, and further to central nodes in the mesocolon. Turnbull was able to improve the results of surgery for colon cancer substantially and it was probably more due to a wide excision of the draining lymph nodes than to the "no touch" technique. This was later accepted as the method of choice but it means that all patients are resected as if they had dissemination of the cancer to lymph nodes. In stage I and II the nodes are thus removed in spite of not being involved by tumour growth.

The importance of microscopic metastatic disease of nodes regarding prognosis is not yet clarified but some investigations in rather small patient materials imply that the outcome is not significantly affected.

In recent years it has become obvious that in rectal cancer surgery the lateral clearance of the mesorectum is crucial to obtain optimal oncologic results which is probably explained by the fact that the mesorectal fatty package surrounding the rectum contains the critical lymph nodes. In rectal cancer total removal of the mesorectum has led to results regarding local recurrence rate that are significantly better than previously reported. This is comparable to the Turnbull concept of colon cancer. Removal of the lymph nodes along the iliac vessels is controversial but it has more and more become apparent that it should primarily be looked upon as a staging procedure. Metastatic disease in those nodes is usually an expression of generalised disease and excision of them does not improve the prognosis significantly. Lymph node surgery tomorrow may be selective and individualised. Micrometastatic disease should be an excellent target for chemotherapy maybe in combination with radiotherapy. Advanced and reliable imaging will be crucial for such decisions. If imaging in the future can detect metastatic lymph node disease also in small nodes the surgery may be tailored for the individual patient. In some cases a rectal cancer may then be treated with local excision combined with radiotherapy. Radioimmunoguided surgery has not yet made such progress that it can be used in common practice but when it becomes more sensitive and more specific it has a great potential. There is, of course, also a theoretical possibility to use antibodies and irradiation not only for diagnostic but also for therapeutic purposes. The concept of the sentinel node has not been applied in colon and rectal cancer but it should be evaluated.

In summary the surgery for colorectal cancer will probably be more differentiated in the future: in some situations it will be more conservative and combined with radio- and/or chemotherapy, but in some it might be more extensive than today.

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Head and neck cancer: From the radical neck dissection (RND) to the selective (SND) and radical modified neck dissection (RMND)

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Lymphatic metastasis in the neck is the single most important prognostic factor directly linked with the risk of distant metastasis and therefore with the survival. Today a number of different cervical lymph node dissection are being used in order to minimize the morbidity of the RND, RMND is used since the 1960's and SND since the 1970's. These procedures spare different Structures such as SCM muscle, accessory nerve, internal jugular vein, Based on a better knowledge of the sites of nodal invasion by function of the primary the SND remove only the neck area (sentinel area) submitted to the risk of nodal metastase. Both of these procedures appear to be safe with a low rate of neck recurrence (NR). Among 97 cases of RMND (1972–78) the NR were 0/40 for N–, 1/21 for N + R–, 3/36 for N+ R+ (Vandenbrouck, 1984). In a recent study of 564 cases of SND (1980–85) we found 34% (136 N+/399 NO) of occult metastasis. The rate of isolated neck failure was low: 20 (6.6%) out of 302 N- and 16 (6.6%) out of 241 N+ with only 12/543 (2.2%) outside the treated neck. When the protocol of treatment was achieved: SND completed in RMND in case of N+ at frozen section examination and/or postoperative radiotherapy.

The SND and RMND are oncologically appropriate tools with low rate of RN and less morbidity than RND. RND keep all his indications for nodes more than 2–3 cm in diameter and moreover for large neck involvement.

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Controversies in breast lymphatic mapping

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The sentinel lymph node is defined as the first lymph node in a regional lymphatic basin that receives lymph flow from a primary tumour. The current status of lymphatic mapping for breast cancer is associated with the following controversies.

(1) False negative rate: Most series report a 5–10% false negative rate. Is this acceptable in oncological terms? How do we ensure a low false negative rate and what is the correct way of calculating the false negative rate?

(2) The learning curve: There appears to be a longer learning curve for those who use blue dye alone compared to those who use blue dye and isotope in combination.

(3) Isotope or blue dye are both: Many methods are described using different isotopes and different routes of administration. Which blue dye and which isotope and the timing and route of administration require further evaluation.

(4) Immunohistochemically positive nodes: The significance of immunohistochemically positive sentinel nodes is unknown. How we should manage these patients is unclear. The value of PCR positive sentinel nodes is even less clear.

(5) Internal mammary nodes: what to do with internal mammary nodes that light up on the lymphoscintigram remains uncertain. The prognostic significance and the value in excising these nodes may need to be re-evaluated in the sentinel node era.

(6) Credentialling for Surgeons: This remains a controversial issue for surgeons in practice.

Sentinel lymph node mapping has established itself as a valid technique in the management of breast cancer, however before it is acccepted as standard of care the aforementioned controversies need to be addressed.

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Sentinel node biopsy in melanoma. Is it worthwhile?

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Lymphatic mapping and sentinel node biopsy is one of the major developments in surgical oncology in this decade. This minimal invasive procedure allows for the identification of clinically occult lymph node metastases, avoiding needless extensive lymphadenectomy. In melanoma patients the technique of sentinel node biopsy is well cristallized, with an identification rate of the sentinel node in 99% of the cases. Reported false-negative basin recurrences, approaching 15% of expected node-positive basins in some series, however, is a matter of concern.

A clear advantage of sentinel node biopsy is that it allows for improved staging, now that the pathologist has the unique opportunity to focus his diagnostic tools on one node only, instead of on a whole dissection specimen. The clinical relevance of this pathological scrutinizing by serial sectioning, immunohistochemistry and the molecular staging technique of RT-PCR for tyrosinase mRNA, however, still has to be proven. The same applies to the intriguing supposition that earlier entry of lymph node positive melanoma patients into adjuvant regimens might be of benefit.

The most crucial question to be answered is, if a positive sentinel node biopsy with subsequent lymph node dissection improves regional tumour control and survival. This issue is at present addressed in a randomized study, initiated by the inventor of the method, D.L. Morton. The outcome of this trial will hopefully bring the long standing debate on the value of elective lymph node dissection to a conclusion. Until then sentinel node biopsy remains an experimental procedure.

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Early stage prostate cancer – Watchful waiting or radical treatment?

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The management of early prostate cancer has been described as the most controversial issue in contemporary oncology. Outcome data are simply too inadequate to allow the formulation of any scientifically wellfounded guideline for decisionmaking. As a corollary, conflicting recommendations have been issued and widely differing treatments used by various professional organizations. The best we can look for is an open debate about issues of a broad range: biological, clinical, ethical, economic, and others. We need to respect differences in opinion while walling for data from randomised, controlled trials.

The management of early stage prostate cancer need also be discussed and understood in the context of screening with prostate specific antigen. Such screening is not only likely to advance the time of diagnosis of cancers that would otherwise have surfaCed clinically at a more advanced stage, perhaps many years later; it may also entail overdiagnosis of histopathologically malignant lesions with limited or no potential to progress to mortal cancer. Since there are no methods available – clinical, histopathologic, molecular, or other – that reliably distinguish mortal cancers from more innocent lesions, the risk for overdiagnosis and overtreatment becomes substantial notably when PSA-screening is used widely.

Given the lack of solid scientific evidence, this lecture will rather address conceptual issues in an attempt to summarize the advantages and the disadvantages of watchful waiting as well as radical local treatment.

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Can surgery provide cure in clinical T3?

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Radical prostatectomy is considered as a standard treatment for locally confined prostate cancer while for locally advanced (cT3) prostate cancer, surgery is traditionally discouraged. These patients have an increased risk of lymph node metastases and local or distant relapse. A combination treatment (radiotherapy with hormonal treatment) is now becoming popular in this particular patient category.

While several reports exist on the outcome of pathologically T3 tumors only few studies have been published on the value of surgery for clinically T3 tumors. Most of the reports have treated patients with combinations of surgery and hormonal treatment. From the available reports (Rotterdam, Würzburg and the Mayo Clinic) it is obvious that there is a high incidence of lymph node involvement. On the other hand these reports have also Shown that surgery can be performed with acceptable morbidity. From our own data, it became obvious that there is a relevant subgroup of clinical T3a patients that are amenable for a curative treatment option by radical prostatectomy. Patients with clinically obvious massive extracapsular extension (cT3b) or seminal vesicle invasion (cT3c) are not good candidates but patients with limited extracapsular extension and a low PSA proved to have a good five year PSA relapse free survival.

These data will need further confirmation in a multi-institutional setting. There is a subgroup of patients with locally advanced disease that can be cured by radical prostatectomy alone. Patients with even more advanced local disease will rather be candidate for a combined radiotherapy-hormonal therapy combination.

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Conformal radiotherapy for prostate cancer

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Three-dimensional conformal radiation therapy (3D-CRT) is a technique of high precision radiotherapy that targets a prescribed dose to the tumor conforming to its spatial configuration, while decreasing the dose to surrounding normal tissues. The latter leads to decreased normal tissue complications, and permits tumor dose escalation to improve local tumor cure. This paradigm was confirmed in a study of 1050 patients with localized prostate cancer treated between October 1988 and March 1998. Prostate biopsies performed at $\geq$2.5 years after radiotherapy showed that patients receiving 81 Gy had 6% positive biopsies, compared with 29% after 75.6 Gy ($p = 0.04$) 43% after 70.2 Gy and 57% after 64.8 Gy. Radiation doses of $\geq$75.6 Gy also significantly improved the 5-year actuarial PSA relapse-free survival. The overall grade 3 rectal and bladder complications was 1.5%. However, the 5-year actuarial risk of grade 2 rectal bleeding for patients receiving 75.6–86.4 Gy was 17% compared to 6% for those treated with 64.8–70.2 Gy ($p < 0.001$). The application of intensity modulated radiotherapy (IMRT) significantly improved the tumor conformality, reduced the exposure of normal tissues, and decreased the rate of grade 2 rectal bleeding. These data indicate that conformal radiotherapy represents an advancement in the ability to deliver the high radiation doses required to improve the local cure of prostate cancer.

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Androgen regulated gene expression in prostate cancer

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Androgens are required for the development of prostate cancer and at least 80% of tumouts respond to androgen deprivation therapy. However, progression to an androgen-independent (AI) state usually occurs and the tumours become increasingly refractory to hormonal manipulation or other therapies.

The mechanisms underlying this transition are unclear but androgen receptor dysfunction, via mutation, amplification or structural changes in the AR protein accounts for some cases although the frequency is controversial. We have examined the CAG microsatellite repents in the transcription activation domain of the AR gene and find limited polymorphism in prostate cancers with a significant predominance of 19 repeats.

We compared the androgen-sensitive cell line LNCaP to a clonal variant, LNCaPr, which is androgen insensitive, to identify differences in the gene expression profile using suppression subtraction hybridisation. Three genes