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Sentinel node biopsy in melanoma

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Lymphatic mapping and sentinel node biopsy have improved staging of patients with melanoma through:

(1) Identification of sentinel nodes outside the traditional regional lymph node basins (in 5.8% of the cases, own series),
(2) Facilitation of the pathologist in microscopical scrutinizing by offering him the very lymph node that reflects the prognostic information of the whole regional basin.

It has been shown that the status of the sentinel node is the strongest prognostic factor in patients with melanoma. In our series of 200 patients with cutaneous melanoma of at least 1.0 mm Breslow thickness, overall survival at three years was 93% if the sentinel node was free of disease and 66% if it was tumour-positive. The definition of a node-negative homogeneous group with a good prognosis who may be spared – experimental – burdensome adjuvant treatment, is one of the most prominent achievements of this novel technique. In this regard the biological relevance of RT-PCR diagnosed 'submicroscopic' disease in the sentinel node is an intriguing issue that needs to be clarified.

The question whether sentinel node biopsy with early removal of involved regional nodes improves survival will probably be answered in the near future by ongoing prospective trials.

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Sentinel node in colorectal cancer

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Intraoperative lymphatic mapping and sentinel node (SLN) biopsy has been accepted as an accurate method to stage melanoma and breast cancer and prevent unnecessary node dissections in these patients. This technology is now being investigated for colon and rectal cancer.

The technique has not as yet been standardized. Some inject blue dye to the colonic serosa either intraoperatively (1) or laparoscopically (2). There are also reports of colonosccopic injection with radiolabeled colloid (3) and even an ex-vivo blue dye injection has been described.

Results have shown a 98.8% success rate of SLN identification with the dye and 83% with the colloid injection, with a false-negative rate of about 9%. In 5% of the patients extraregional drainage was identified. A pilot pathologic study using immunohistochemistry (IMH) and RT-PCR identified micrometastasis in an additional 10% of the patients by IMH and an additional 40% by RT-PCR.

Two important questions yet to be answered in order to assess the possible benefit of the technique are (i) whether SLN can increase staging by conventional pathology and (ii) whether micrometastasis identified by IMH has clinical significance and what exactly is the clinical role of RT-PCR.

The technique and results will be presented, the controversy discussed and future studies will be suggested.

References

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Sentinel nodes in gynecology

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In recent years there has been intense interest amongst gynecologic oncologists in developing lymphatic mapping procedures in patients with vulvar and cervix cancer. Squamous carcinoma of the vulva and cervix are good targets for the lymphatic mapping strategy. Most node positive patients have regional disease and chemoradiation has improved the outcome for these patients. There have been several published series regarding lymphatic mapping in patients with vulvar cancer. Investigators have described the use of blue dye alone, radiolocalization alone, as well as combining these two techniques. The consensus appears to be that the combined technique is ideal since it requires the shortest learning period, can help select patients for unilateral versus bilateral dissection, and has a very high sentinel node identification rate. In published series the false negative rate has been very low in patients undergoing the combined procedure. At present, there is a large validation study going on in North America sponsored by the Gynecologic Oncology Group and a prospective observational study going on in the Netherlands for patients undergoing sentinel node biopsy alone.

Cervix cancer is a much more common disease; however, the benefits of lymphatic mapping are not quite as clear as with vulvar cancer. Lower extremity lymphedema is common in patients who undergo full groin dissection. Lymphedema of the lower extremities in patients undergoing radical hysterectomy occurs much less commonly. Nevertheless, investigators have sought ways of identifying sentinel nodes in patients with cervix cancer in part with the goal of selecting node positive patients for a combined modality treatment. There has been a handful of clinical trials describing lymphatic mapping in patients with cervix cancer; all of these have used combined techniques. Investigators in France and Germany have both emphasized the utility of combining operative laparoscopy with sentinel node biopsy. The recent development of laparoscopic gamma probes is aiding in this effort. The published experience with sentinel node identification in patients with cervix cancer is small, however it is anticipated in the next few years this will change and investigators will seek ways of incorporating sentinel node biopsy into the management in patients with cervix cancer.

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Sentinel node in breast cancer

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The concept of the the sentinel node (SN) in breast cancer being the first lymph node on a direct drainage pathway from the tumour site has been widely accepted.The node can be localized and the suggestion that the SN is representative for the nodal status has been confirmed by a number of studies across the world.

The end-points of evaluation of the method will be locoregional axillary relapse as well as overall and disease-free survival compared to patients with routine axillary clearance. Studies with a follow up of 5-10 years have not been reported yet.

Patients with unifocal tumour less than 3 cm and clinically normal axilla are eligible for sentinel node biopsy (SNB).

It is to prefer a combination of injection of radioactive tracer, preoperative lymphoscintigraphy, dye injection and intraoperative identification by gamma-probe and visualization of blue nodes. Intra- or peritumoural injection seems the best, because it gives more complete mapping with extra-axillary nodes as well. In order to prevent reoperations intraoperative frozen section examination of SN should be accurate to minimize the number of nodes being positive in the postoperative evaluation.

Cost-benefit aspects indicate also that SNB is most valuable in patients with low risk of positive nodes due to small non-palpable tumours.

In hospitals starting SNB the team should perform and audit study. A widely accepted number of cases is 30 with over 90% success rate and less than 5% false negatives. However, this design os not founded on principles of statistical power.Audit studies may be avoided in the future by tutoring surgeons in centres with documented quality.

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Sentinel node in prostate and bladder cancer

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In prostate and bladder cancer, as in most cancer forms, lymph node metastasis is considered a sign of systemic disease. Curative treatment is most often impossible in such cases, and major ablative surgery or full-dose irradiation may be contraindicated if the patient has no local symptoms of his malignant disease. An adequate lymph node staging prior to undertaking the curative treatment is thus mandatory.

In prostate and bladder cancer, the standard lymph node staging procedure is performed either as an open procedure or laparoscopically, and comprises the excision of the obturator and sometimes internal iliac nodes for histopathologic examination. These nodes are considered as the regional nodes of those organs and the most common locale for metastasis.

However, the knowledge on the lymphatic drainage of this area is largely based on older anatomical studies and some reports do point out that, in fact, from 10 to 30% of cases may have metastasis-free obturator nodes and later are diagnosed with node metastasis more cranially, i. e. common iliac and paraaortic nodes.

More recent studies with isotope scans combined with intraoperative scintillation-counter and colour dye detection of suspicious nodes verify the

abovementioned findings and may facilitate a more limited and focused node dissection, avoiding dissection of unnecessary areas.

In conclusion, new knowledge in this field is challenging the standard lymph node staging procedures, i.e. obturator node dissection, as the sentinel nodes are often found farther away from the primary tumor site. To avoid extensive lymph node dissections with their concomitant morbidity, the novel techniques described will be useful, but further refinements will be necessary and are doubtlessly underway.

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Intra-arterial cisplatin and concomitant radiation for inoperable head and neck cancer

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Purpose: To determine the feasibility and effectiveness of intra-arterial cisplatin with concomitant radiotherapy (RADPLAT) for locally advanced, inoperable stage IV, squamous cell carcinoma of the head and neck.

Patients and Methods: From April 1997 to December 1999, eighty-five patients with locally advanced head and neck carcinoma were treated with radiotherapy (70 Gy, 7 weeks, 35 fractions) and concomitant supra-selective intra-arterial cisplatin (150 mg/m2, day 1, 8, 15, 22) and systemic sodium thio-sulfate rescue (RADPLAT). Main inclusion criteria were: inoperable squamous cell carcinoma of the head and neck or cancer requiring total glossectomy, any N, M0, Karnovsky performance status at least 60%, no prior surgery, radio- or chemotherapy. The median age was 50 year (40–69). Tumor characteristics: 75 patients had a T4 tumor, 10 T3, (3–10 cm), 61 had N+ disease, (1–10 cm).

Results: All patients received the scheduled treatment. Complete remission was achieved in 90%. At 40 months: Disease free survival, Locoregional Control and Local Control were 50%, 62% and 68% respectively. No treatment interruptions or dose limitations resulted from acute toxicity. One patient had a treatment-related death. Seventeen percent had grade IV (CTC) hematological toxicity, no other grade IV side-effects were seen. Grade III acute toxicity (RTOG): mucositis in 43%, upper GI in 60%, hearing loss in 10%.

Conclusion: The RADPLAT treatment schedule is feasible with excellent response rates and organ preservation. Based on the results of this study, a multicenter phase III trial comparing radiotherapy and concomitant systemic cisplatin versus RADPLAT is ongoing.

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Postoperative Combined Radiation and Chemotherapy Improves Disease-Free Survival (DFS) and Overall Survival (OS) in Resected Adenocarcinoma of the Stomach and G.E. Junction. Results of Intergroup Study INT-0116 (SWOG 9008)

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The cure rate for patients with resected gastric cancer is 5% - 40%. INT-0116 was designed to evaluate post-operative adjuvant chemoradiation in resected gastric cancer.

Study Design: Patients with stages Ib through IV M0 adenocarcinoma of the stomach or gastroesophageal junction who had undergone gastric resection with curative intent were randomized to postoperative follow up or chemoradiation. The treatment consisted of one cycle of 5-FU (425 mg/m*)/Leucovorin (LV) (20 mg/m*) in a daily x5 regimen followed by 4,500 cGy (180 cGy/day) given with 5-FU/LV (400 mg/m* and 20 mg/m*) on days 1 through 4, and on the last 3 days of radiation. One month after completion of radiation, two cycles of daily x5 5-FU/LV (425 mg/m* and 20 mg/m*) were given at monthly intervals.

Results: Between 8/1/91 and 7/15/98, 603 patients were accrued to this study, 47 (8%) of which were ineligible. Nodal metastases were present in 85% of cases. The combined modality regimen in this program was tolerable. There were 3 (1%) toxic deaths. Grade 3 and grade 4 toxicity occurred in 41% and 32% of cases, respectively. The gr. 3 toxicities were: hematologic (54%), GI (33%), infection (6%), neurologic (4%). OS and DFS analyses were based on intention to treat. With 3.3 years of median follow up, 3-year DFS is 49% for treatment and 32% for observation (p=0.001); 3-year OS is 52% for treatment and 41% for observation (p=0.03).

These results demonstrate a 44% improvement in relapse-free survival (hazard ratio of 1.44), and a 28% improvement in survival with median survival of 27 months in the observation arm vs. 42 months in the treatment arm (hazard ratio 1.28). Postoperative chemoradiation may now be considered a standard of care for high-risk R0 resected locally advanced adenocarcinoma of the stomach and GE junction.

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Radiochemotherapy is more effective than dose escalation in locally advanced head and neck cancer: results of a german multicentre randomized trial

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Purpose: Is accelerated chemoradiation more effective than accelerated radiotherapy alone?

Methods: Between March 1995 and May 1999, 384 patients with locally advanced H&N cancer were recruited for this multicentre study from 10 German centers. Male/female ratio was 82%/18%, mean age was 55 years. The oropharynx (60.4%) and hypopharynx (32.3%) were the predominant tumour sites, oral cavity tumours accounted for only 7.3% of all tumours. 5.5% and 94.5% of all tumours were stage III and IV, respectively. All patients with stage III- and IV-disease lacking evidence of distant metastases qualified for the treatment. Three target voumes (TV) were defined as follows: 1. Macroscopic tumour and lymph nodes 2. High-risk regions for lymphatic spread 3. Low-risk areas of lymphatic spread. The overall treatment time in both study arms was 6 weeks (40 days). The fractionation in study arm A was 14 Gy/2 Gy q.d. and b.i.d. 1.4Gy to a total dose of 77.6 Gy. Mitomycin C on days 5 and 36 @ 10mg/m* and 350 mg/m* 5-FU as bolus plus a 120 hrs. continuous infusion of 600 mg/m* 5-FU were additionally applied.

Results: The median follow-up was 30 months for all patients. The absolute values of locoregional failures in arm A vs. B were 49.7% vs. 37.6% (p=0.03). The total no. of metastases did not differ with 30.6% (arm A) vs. 34.9% (arm B). Actuarial locoregional control values were 46.4% (arm A) vs. 57.0% (arm B) @ 2 years (p=0.03). The hazard ratio (HR) was 0.72 (CI: 0.53-0.98). The overalll survival rates were 39.1 (arm A) vs. 49.4% (arm B) @ 2 years (p=0.05). The HR was 0.80 (CI: 0.62-1.04). None of seven parameters tested for acute grade 3 and 4 morbidity were statistically different in both treatment arms. Of 12 parameters tested for late grade 3- and 4 morbidity, only dysphagia (p=0.01) turned out to be pronounced in treatment arm A.

Conclusions: These results give evidence that accelerated radiotherapy of 70.6 Gy plus MMC/5-FU is superior to 77.6 Gy of accelerated fractionation alone in terms of locoregional control and overall survival at equitoxic levels of acute and late radiation morbidity.

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Concurrent chemo/radiotherapy in cervical cancer. What don't we know?

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Radical radiation therapy had been the accepted standard of care for advanced cervical cancer. In February 1999 the U.S. NCI issued a rare Clinical Announcement: "..five randomized phase III trials show an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy." "..strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer."

The trials compared various doses and schedules of concurrent cisplatin-containing chemotherapy to pelvic irradiation alone, extended field irradiation or radiation and hydroxyurea. A similar reduction in the relative risk of death was observed. Absolute survival benefits ranged between 9 and 18%. These and other relevant studies including the two large randomised Canadian studies showing no detectable benefit will be reviewed.

The data suggest that the optimal regimens of concurrent chemoradiation are ill defined and may not be the "standard" of weekly cisplatin. A large study using oral 5-FU and Mitomycin has demonstrated benefit, as did one using Epirubicin. One study did not show benefit with concurrent infusional 5-FU when added to optimized radiation.

The Canadian study of pelvic irradiation with or without concurrent weekly cisplatin did not show survival benefit. The relative risk of death with concurrent therapy was 0.91. A number of possible explanations may