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TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER

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The FIGO Committee has decided not to replace the clinical staging for cervical cancer. The presence of lymph node metastases is the most important prognostic factor and lead to a decreased overall survival from about 85% to 65%. Reliable information on these factors is necessary for a stage adjusted therapeutic decision making. Our group published data on 100 patients, which demonstrated a survival benefit for lymph node positive patients who underwent Tran peritoneal laparoscopic staging prior to chemoradiation. There was a surgical staging in 555 and a clinical (including radiographical) staging in 130 patients. Latter patients had a better performance status and a smaller tumour size compared to those with surgical staging.

Keywords: cervical cancer., chemoradiation

Clinical Staging. The FIGO Committee has decided not to replace the clinical staging for cervical cancer. The presence of lymph node metastases is the most important prognostic factor and lead to a decreased overall survival from about 85% to 65%.

Reliable information on these factors is necessary for a stage adjusted therapeutic decision making. Histologically confirmed pelvic lymph node metastases indicate the use of chemoradiation and showed that the patient might not benefit from a radical surgery. Patients with proven paraaortic lymph node metastases have a worse prognosis compared to those with pelvic lymph node metastases only. The use of extended field radiation in the context of chemoradiation leads to long term survival rates between 35-50%. Nearly all patients with unknown and *untreated* paraaortic lymph nodes will die. On the other side, patients with intraperitoneal spread would not benefit from a definitive chemoradiation.

Surgical Staging. Surgical staging for cervical cancer has been discussed controversially for more than 30 years. Up to now, no randomized trial could demonstrate a survival benefit for surgical staging prior to chemoradiation. There is retrospective data that the therapeutic concept was modified by the results of the surgical staging in a considerable number of patients. Furthermore, our group published data on 100 patients, which demonstrated a survival benefit for lymph node positive patients who underwent Tran peritoneal laparoscopic staging prior to chemoradiation [*Marnitz S. et al., 2005*]. Pooled data [*Gold M. et al., 2008*] from randomized phase III trials of chemoradiation in cervical cancer patients (GOG 85, 120, 165) were analyzed with regard to the staging procedure prior to (chemo)radiation. There was a surgical staging in 555 and a clinical (including radiographical) staging in 130 patients. Latter patients had a better performance status and a smaller tumour size compared to those with surgical staging. Surgically staged patients with stage III/IV showed a significantly better overall survival with 54.3% compared to the clinical staging group with 40%. There were 31.9% paraaortic failures in the clinical staging group and 15.1% in the surgical group.

The largest benefit from pre-treatment surgical staging is expected in stage IIB-IV cervical cancer patients because of the incidence of paraaortic lymph node metastases ranging from 20 to 30%. The only randomized study on this issue is now recruiting patients [*DEGRO*].

Primary Chemoradiation. After the publication of five randomized trials in 1999, the NCI issued an alert chemoradiation should be performed in cervical cancer patients instead of radiation. Two systematic reviews demonstrated improved survival, progression free survival

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with chemoradiation. The interpretation of these results is complicated by the use of different treatments, chemicals, target volumes for radiation and different diagnostic and surgical procedures. The MRC initiated a systematic review and metaanalysis in order to collect and validate individual patient data. The inclusion criteria were limited to trials comparing concomitant chemoradiation to the same radiation alone.

On the basis of the available data, patients were 35-64 years old with FIGO stage IIB (35%) or III (36%) tumour. The paraaortic nodal status was either unknown (51%) or uninvolved (48%). Patients with histologically confirmed paraaortic metastases were excluded from this analysis.

The analysis was restricted to 13 trials. There was an absolute disease free survival benefit of 8% after 5 years (50 versus 58%), of 5 year loco regional disease free survival of 9% and metastases free survival of 5%. Based on two small trials, larger benefits could be demonstrated for trials with additional chemotherapy after chemoradiation, with an absolute improvement of 19% at 5 years.

The authors found no evidence of a difference in the size of the effect of chemoradiotherapy when trials were grouped according to the type of chemotherapy, the cycle length or dose intensity of chemotherapy. Although the effect of chemoradiation seems consistent across patient subgroups defined by age, histology, grading, lymph node involvement, there was a trend of a decreasing benefit of chemoradiation with increasing tumour stage. There was a significant increase in higher grade GI toxicity for the groups of trials using platinum based chemoradiotherapy. This increase was not observed in trials using non-cisplatinum chemoradiation, where the incidence of GI toxicity was low in both arms nor in trials using hydroxyurea in the control arm, where the incidence of severe GI toxicity was high in both arms (approximately 10%). 1-3% of all patients experienced severe late toxicity, but data on late toxicity were nor recorded for the majority of patients [*Reducing Uncertainties*, *2008*].

The role of “new substances” in the primary treatment is still undefined.

In order to minimize therapy related toxicity, 3D conformal therapy should be used for external beam radiotherapy (EBRT). More sophisticated radiation techniques like intensity modulated radiation therapy or helical tomotherapy are able to decrease the dose to the surrounding normal tissue. For IMRT it has been shown, that the decreased dose to the normal tissue could be translated into a decreased acute and late toxicity. Helical tomotherapy provides more homogeneity and conformity in dose distribution in the target volumes. The aim of using modern techniques is not only to minimize acute and late toxicity, but also dose escalation and an improved locoregional control without the increased toxicity.

In contradiction to the primary staging in cervical cancer patients, PET-CT can provide useful information in patients with recurrent cervical cancer. It may help to define a small radiation volume which is important because of previous surgery and/or radiation therapy.

Up to now, brachytherapy should be an integral part of the combined primary treatment of patients with cervical cancer. A wide range of fractionation schemas has been reported. Although only retrospective data underline the correlation between total dose and local control in cervical cancer, biologically effective doses of 75-85 *Gy* seem to be necessary in order to eradicate cervical cancer. Because of the correlation of local control rate and the treatment duration, the American Brachytherapy Society recommends duration $\leq$ 56 days. Either low dose rate, pulse dose rate or high dose rate brachytherapy can be used.

Efforts should be made to preserve the ovary function. In patients with squamous cell carcinoma the incidence or ovary metastases is about 0.5%, whereas ovary metastases occur in 6% of patients with adenocarcinoma. A transposition of the ovaries prior to chemoradiation and the use of modern techniques for sparing the organ at risk might preserve the ovarian function in about 50% of the patients.

Adjuvant Chemoradiation.

There are some risk factors defined for a poorer oncological outcome: Pelvic and/or para-aortic lymph node involvement, parametric infiltration, lymphovascular space involvement, haemangiosis, bulky primary and R1/2 resection. After surgery, in theses cases, adjuvant chemoradiation is indicated. There is no valid data available for the use of sequential chemotherapy after adjuvant chemoradiation. Concerning techniques and chemotherapy see chapter primary chemoradiation. Up to now, no subgroup has been defined which might benefit from adjuvant radiation therapy alone. Because of the higher incidence and severity of late toxicity, a combined approach of hysterectomy and chemoradiation should be avoided. The patients should be selected by a pre-treatment laparoscopic staging for a radical hysterectomy OR chemoradiation.

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