

**Pathologic Complete Remission after Preoperative High-Dose-Rate Brachytherapy in
Patients with Operable Cervical Cancer**

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The role of preoperative high-dose-rate (HDR) brachytherapy (BT) in the treatment of early stage cervical cancer (ESCC) is controversial. The purpose of my theses was to explore the efficacy and potential advantages of preoperative HDR BT in the multidisciplinary management of ESCC in a prospective multicentric randomized study.

Between May 2005 and March 2012, 185 patients with operable ESCC (stage I/A2-II/B) were randomized to receive either preoperative intracavitary HDR BT of 16 Gy in 2 fractions (arm “A”; n=88) or no preoperative BT (arm “B”; n=97). Seventy out of 88 (80%) arm “A” and 80 out of 97 (82%) arm “B” patients underwent radical Wertheim (Piver III) hysterectomy. Adjuvant treatment was indicated and administered according to prospectively defined risk groups: for low risk patients no postoperative treatment was given, medium risk patients received external beam pelvic radiotherapy combined with vaginal BT, the high-risk group was treated with radio-chemotherapy.

We aimed to assess the efficacy of preoperative HDR BT by:

1. comparing the rate of pathologic complete remission (pCR) after preoperative HDR BT with the rate of negative specimen found in patients treated with primary surgery
2. comparing the mean size of residual tumors in the two arms
3. comparing the rate of negative surgical margins in the two arms
4. comparing the rates of relapse free survival (RFS), distant metastases free survival (DMFS), and overall survival (OS) in the two arms

The aims of the pathologic examinations were:

5. Evaluating the role of different immuno-histochemical (IHC) reactions in the differential diagnosis (determining the invasiveness or the exact histological type of the tumor)
6. Identifying the presence and prognostic significance of HPV in an indirect way with the p16 reaction
7. Investigating the possible role of tumor suppressor genes p53 and p21 as predictors for

the radiosensitivity of cervical cancer

Results:

1. The pCR rate was 25.7% after preoperative HDR BT, while it was only 11.2% with surgery alone ($p=0.03$)
2. The mean tumor diameter at pathologic examination was 25.7 mm after preoperative BT, and 29.3 mm without preoperative treatment ($p=NS$)
3. The rate of positive surgical margins was 1.5% after preoperative BT, while it was 11.4% without preoperative BT ($p=0.02$)
4. At a mean follow-up period of 29 months there was no significant difference in the 5-year estimates of RFS (0.94% vs. 0.96%) and DMFS (0.92% vs. 0.88%). The difference in 5 year-OS between the two arms was non-significant (85.2% vs. 81.9%), but there was a tendency for better OS in patients with pCR versus non-pCR patients (91.8% vs. 81.5%; $p=0.31$)
5. The IHC reaction laminin provided significant help in the differentiation between in situ and invasive tumors. Expression of p63 was highly specific for squamous differentiation, which was useful in the differential diagnosis of squamous cell carcinomas versus adenocarcinomas. CK7 reaction did not prove to be a specific marker for glandular differentiation.
6. The ratio of p16 IHC positivity was 100%, so we could not examine the prognostic significance of p16 positivity and HPV infection in cervical cancers.
7. Tumor regression was correlated neither with the intensity of p53 and p21 reactions, nor with the staining for p16, so we cannot use them as predictors for radiosensitivity.

Conclusions: Preoperative intracavitary HDR BT significantly increases the rate of pCR and decreases the incidence of positive surgical margins in patients operated for ESCC. Longer follow-up is required to establish the possible impact of pCR on the ultimate rate of OS. However, a non-significant tendency towards better survival in the group of patients with negative surgical specimen was observed. Laminin proved to be a reliable marker in determining the invasiveness of a tumor, p63 was specific for squamous differentiation, CK7 did not prove to be specific for glandular differentiation. None of the IHC markers examined (p53, p21, p16) predicted radiosensitivity.