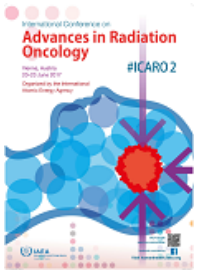


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# Dose-volume effects in pathologic lymph nodes in cervical cancer

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**Purpose/Objective.**
The advent of intensity-modulated radiotherapy (IMRT) and image-guided adapted brachytherapy (IGABT) has allowed for safe delivery of higher doses in the treatment of locally advanced cervical cancer, translating to better local control. Moreover, nodal boosts are increasingly being used in order to improve regional control. However, while dose-volume relationships have been defined for the primary tumor and organs at risk, the optimal dose threshold for the treatment of pathologic lymph nodes remains uncertain. The objective was to identify planning objectives for pathologic nodes.

**Material and Methods.**
Patients with node-positive non-metastatic cervical carcinoma treated curatively with combined external beam radiotherapy (EBRT) and IGABT were identified. Pelvic EBRT was carried out to 45.0 - 46.0 Gy, using three-dimensional conformal radiotherapy (3DCRT) or IMRT techniques, with concomitant chemotherapy. Nodal boosts were performed sequentially or using the simultaneous integrated boost (SIB) technique depending on the EBRT technique used. IGABT was conducted within two weeks after completion of pelvic EBRT, using pulsed-dose rate (PDR) techniques and personalized vaginal mold applicators.
The contributions of EBRT, IGABT (D98) and nodal boosts were converted in 2-Gy equivalent ($\alpha/\beta$=10 Gy) and summated. The nodes were individually followed from diagnosis to relapse. Resected nodes during para-aortic node surgical staging were not considered. Statistical analyses comprised log-rank tests (univariate analyses), Cox proportional model (factors with $p \leq 0.1$ in univariate), and Probit analyses.

**Results.**
One hundred and fifteen patients were included, with a total number of nodes of 288 (2.5 per patient). All patients had a staging CT and MRI. PET-CT was performed in 90.6% of the patients; para-aortic dissection in 53.8%. Histologic subtypes comprised squamous cell carcinomas (SCC) in 88.9%, adenocarcinomas in 8.5% and adenosquamous in 2.6%. The mean pathologic node volume at diagnosis was 3.4±5.8 cm3. The mean EBRT and nodal boost doses were 44.3±0.9 Gy and 10.0±2.9 Gy respectively. The mean IGABT contribution to pelvic nodes was 4.2±2.6 Gy. Finally the mean total dose to lymphadenopathies was 55.3±5.6 Gy. Concomitant chemotherapy was administered in 96.5% of the patients. After a median follow-up of 33.5 months, 20 patients (17.4%) experienced relapses in nodes initially considered pathologic at diagnosis (local relapse). Among them, recurrences were observed in a total of 44 nodes (15.3%). The mean time from treatment completion to relapse was 9.0±11.8 months.
There was no significant relationship between the dose delivered to pathologic nodes and local control probability (p=0.38). Univariate analyses tested various factors: subtypes (SCC versus others, p=0.35), concomitant chemotherapy (p=0.39), use of SIB (p=0.07), volume at diagnosis (threshold: 3 cm3, p<0.0001) and dose ($\geq$ 57.5 Gy, p=0.039). The last three factors were entered in a multivariate analysis. Volume (HR=8.2, 4.0-16.6, p<0.0001) and dose (HR=2, 1.05-3.9, P=0.034) remained independent, whereas SIB was not (p=0.99). Subsequent Probit analysis combining dose and volume showed significant relationships with the probability of local control (Figure).

**Conclusion.**
The initial volume was the main prognostic factor of control in pathologic lymph nodes. A dose superior to 57.5 Gy was also associated with a better local control probability. Further studies are required to refine these findings.

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