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Dose-volume effects in pathologic lymph nodes in locally advanced cervical cancer

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HIGHLIGHTS

- Image-guided radiotherapy has allowed for nodal boosts in cervix cancer.
- Dose-volume effects in involved nodes in cervix cancer are shown for the first time.
- There is increasing control benefit of dose-escalation with higher nodal volumes.
- However, nodal control probability is <70% with volumes >15 cm^3.

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ABSTRACT

Objective. In cervical cancer patients, dose-volume relationships have been demonstrated for tumor and organs-at-risk, but not for pathologic nodes. The nodal control probability (NCP) according to dose/volume parameters was investigated.

Material and methods. Patients with node-positive cervical cancer treated curatively with external beam radiotherapy (EBRT) and image-guided brachytherapy (IGABT) were identified. Nodal doses during EBRT, IGABT and boost were converted to 2-Gy equivalent ($\alpha/\beta = 10$ Gy) and summed. Pathologic nodes were followed individually from diagnosis to relapse. Statistical analyses comprised log-rank tests (univariate analyses), Cox proportional model (factors with $p \leq 0.1$ in univariate) and Probit analyses.

Results. A total of 108 patients with 254 unresected pathological nodes were identified. The mean nodal volume at diagnosis was 3.4 ± 5.8 cm^3. The mean total nodal EQD2 doses were 55.3 ± 5.6 Gy. Concurrent chemotherapy was given in 96%. With a median follow-up of 33.5 months, 20 patients (18.5%) experienced relapse in nodes considered pathologic at diagnosis. Overall nodal recurrence rate was 9.1% (23/254). On univariate analyses, nodal volume (threshold: 3 cm^3, $p < .0001$) and lymph node dose (≥57.5 $Gy_{\alpha/\beta 10}$, $p = .039$) were significant for nodal control. The use of simultaneous boost was borderline for significance ($p = .07$). On multivariate analysis, volume (HR = 8.2, 4.0–16.6, $p < .0001$) and dose (HR = 2, 1.05–3.9, $p = .034$) remained independent factors. Probit analysis combining dose and volume showed significant relationships with NCP, with increasing gap between the curves with higher nodal volumes.

Conclusion. A nodal dose-volume effect on NCP is demonstrated for the first time, with increasing NCP benefit of additional doses to higher-volume nodes.

1. Introduction

Current radiotherapy practice incorporating image-guided brachytherapy (IGABT) techniques results in excellent local control (LC) rates, however regional control (RC) rates remain suboptimal [1–6].

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The use of simultaneous integrated nodal boost (SIB) to doses of at least 55–60 Gy has been shown to be associated with high RC rates [7,8]. This approach is advantageous in that it avoids prolongation of overall treatment time and the additional dose is given at the same time as the chemotherapy. However, this may potentially increase acute toxicity and late morbidity, and the additional dose might limit adequate delivery of brachytherapy doses to the primary tumor.

Another approach is the sequential nodal boost (SEB), which may be associated with less toxicity due to its conventionally fractionated schedule, but may be associated with prolonged overall treatment time with regards to the pathologic nodes. Furthermore, it could allow for a more adaptive strategy if boost dose can be tailored according to interim response [4], and brachytherapy (BT) nodal dose, if the boost is given post-BT.

With the use of IGABT and interstitial brachytherapy (ISBT) techniques, BT-contributed dose becomes increasingly significant and varies considerably among nodal groups and between techniques, applicator and dose rate employed [9–12]. For example, using personalized vaginal mold applicators (VMA) in pulsed-dose rate (PDR) IGABT leads to higher pelvic nodal doses as compared to those reported in high dose-rate (HDR) BT series, partly because the use of VMA is associated with a configuration that displaces the high dose-gradient areas closer to the obturator and internal iliac nodal regions [12].

We sought to examine the effect of nodal dose and volume, as well as other clinical and treatment factors, on nodal control, and to describe first-event failures among node-positive cervical cancer patients treated with chemoradiation, with or without nodal boost, and PDR IGABT.

2. Materials and methods

2.1. Patient selection

Consecutive cervical cancer cases treated at our institution from 2002 to 2011 and fulfilling the following criteria were identified and reviewed: squamous cell, adenosquamous or adenocarcinoma histology, intact uterus, node-positive non-metastatic disease (para-aortic node metastases below L1-L2 allowed), treated definitively with EBRT ± concurrent chemotherapy and IGABT, with minimum 3-month follow-up after brachytherapy completion.

2.2. Pretreatment evaluation and nodal staging

Abdominopelvic CT, pelvic MRI and/or positron emission tomography – computed tomography (PET-CT) scan were used for nodal staging and were centrally reviewed in multi-disciplinary meetings involving expert radiologists. Pathologic nodes were defined as having any of the following: short-axis diameter of ≥10 mm; rounded shape, heterogeneous enhancement, and/or significant PET uptake (relative to the noise and primary tumor uptake).

From 2007, a laparoscopic para-aortic node dissection (PAND) was performed as part of primary staging in patients without para-aortic lymph node uptake on PET-CT to eliminate false-negatives and guide radiotherapy fields [13–14]. Surgically removed pathologic nodes were excluded from our analysis.

2.3. External beam radiotherapy

EBRT was delivered using high-energy photon radiotherapy and 3DCRT or IMRT techniques. Pelvic EBRT was carried out to 45.0–46.0 Gy in 1.8–2.0 Gy fractions. The centro-pelvic clinical target volume (CTV-T) included the gross tumor volume (GTV), the cervix, the whole uterus, the adnexa when visible, the parametria, and at least the upper half of the vagina, or lower, depending on tumor involvement. The nodal CTV (CTV-N) encompassed the bilateral common iliac, external iliac, internal iliac, obturator and the presacral nodal vessels with 7–10 mm margins. The inguinal nodal areas were included in case of involvement of the distal third of the vagina. The para-aortic area was irradiated in patients with documented involvement on PET-CT or PAND, up to the T12-L1 or T11-T12 level, depending on the highest pathologic node. To generate the planning target volume (PTV), a margin of at least 10 mm was added in all directions around the CTV-T and 7 mm around the CTV-N. Concurrent chemotherapy was delivered, cisplatin 40 mg/m^2 weekly, or carboplatin in case of renal impairment.

The modalities of boost delivery depended on the EBRT technique. Patients treated with 3D conformal EBRT received SEB. In this case, a replan was performed after BT to guide the lymph node boost delivery and dose prescription took into account the cumulative contribution of EBRT and BT dose contribution, in order to achieve a total target physical dose of ≈55–60 Gy. Boost could be also withdrawn in case of small initial node volumes, when cumulative EBRT-BT dose was deemed sufficient, or when there was complete remission of lymph nodes at time of BT, depending on the physician judgment.

From 2010, there was an increasing use of IMRT in our center. Patients treated with IMRT received a SIB to unresected pathologic nodes, with objective to deliver a target physical dose of approximately 60 Gy, taking into account the expected contribution of BT. Based on previous dosimetric studies, this contribution is estimated to be approximately 5 Gy for lower pelvis lymph nodes, 2.5 Gy for common iliac lymph nodes, and negligible for para-aortic lymph nodes. Therefore, SIB prescription dose was 55 Gy in fractions of 2.2 Gy for obturator, internal iliac or external iliac lymph nodes, 57.5 Gy in fractions of 2.3 Gy for common iliac lymph nodes, and 60 Gy in fractions of 2.4 Gy for para-aortic lymph nodes [12].

2.4. Brachytherapy

All patients underwent brachytherapy at our institute. PDR IGABT was delivered following EBRT keeping overall treatment time < 55 days, if possible. A personalized VMA and an intra-uterine catheter were inserted under general anesthesia. Three-plane, T2-sequence MRI simulation scans with 3 mm-thick slices were acquired, with dummy sources in place to facilitate applicator reconstruction [15]. Alternatively, 3 mm-thick, contrast-enhanced CT simulation scans were obtained. High-risk and intermediate-risk clinical target volumes (HR-CTV and IR-CTV) as defined by the GEC-ESTRO (*Groupe Européen de Curiethérapie* – European Society for Radiotherapy and Oncology) and OAR (bladder, rectum, and sigmoid) were delineated [16]. Planning objectives were to deliver cumulative EQD2 doses (summed EBRT- and BT-delivered 2-Gy equivalent doses, applying the linear quadratic [LQ] model using $\alpha/\beta = 10$ Gy and a half-time repair of 1.5 h) of ≥85 $Gy_{\alpha/\beta 10}$ and ≥60 $Gy_{\alpha/\beta 10}$ to 90% of the HR-CTV and IR-CTV, respectively (D90 HR-CTV, D90 IR-CTV). Dose constraints were cumulative EQD2 doses of <75 $Gy_{\alpha/\beta 3}$, <75 $Gy_{\alpha/\beta 3}$, and <85 $Gy_{\alpha/\beta 3}$ to the maximally exposed 2 cm^3 volumes (D^3_{2cm}) of the rectum, sigmoid, and bladder, respectively (LQ model, $\alpha/\beta = 3$ Gy). Dosimetry was performed using a standard loading pattern relative to the delineated IR-CTV and a prescription of 15 Gy normalized to point A was used as starting point of the optimization process, then manual optimization was done to meet the objectives in terms of HR-CTV coverage and OAR dose constraints described above.

2.5. Total nodal dose

We retrospectively determined the total physical doses received by all individual pathological nodes, during EBRT and BT. For cases treated with EBRT in other institutes, staging CT, MRI and/or PET as well as detailed EBRT dosimetry data were recovered to determine nodal doses.

To estimate BT nodal dose contribution, each pathologic node identified prior to EBRT was individually contoured on the BT simulation MRI or CT and the dose delivered to 98% of each nodal volume (D98) was noted [12]. For nodes with complete response (CR) after pelvic

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