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Controversy

Definition of lymph node areas for radiotherapy of prostate cancer: A critical literature review by the French Genito-Urinary Group and the French Association of Urology (GETUG-AFU)

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ABSTRACT

Purpose: Recommendations for pelvic lymph node (LN) contouring rely on relatively dated studies that defined the Clinical Target Volume (CTV) of interest proposed for radiotherapy. The aim of this article was to review these recommendations with a critical analysis of published data on prostate cancer drainage.

Methods: We performed a review of data on LN drainage in prostate cancer, based on anatomy texts and studies on lymphography, pelvic LN dissections, sentinel LN techniques, magnetic resonance imaging, computed tomography and functional imaging. We also present the GETUG experts' opinion, based on a survey on nodal CTV definition.

Results: For lymphatic drainage of prostate cancers, pelvic LN areas classically considered are: distal common iliac, external iliac, internal iliac and obturator regions. Recently published data allow a mapping of sites at risk of pathological LN invasion. In 10–70% of cases, these sites are not included in the pelvic LN CTVs defined in consensuses. In accordance with other cooperative groups, the GETUG experts' survey showed that proximal common iliac, para-aortic, para-rectal and pre-sacral regions could include sites at risk of invasion in extended LN CTV, but were not considered in CTV contouring common practice. New recommendations are needed for nodal CTV in radiotherapy of prostate cancer.

Conclusions: The assessment of the efficacy and safety of LN radiotherapy is still the subject of several randomised studies. Whether or not meaningful results are obtained depends directly on the quality and homogeneity of the data analysed. A new consensus for delineation of LN regions appears necessary.

Introduction

External beam radiation therapy (EBRT) is a standard of care in prostate cancer [1]. Endocrine treatment, with or without EBRT, was evaluated in 3 randomized studies [2–4]. The SPG-7/SFUO-3 trial [4] did not include lymph node (LN) irradiation in contrast

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with the recently updated NCIC CTG PR3/MRC PR07 study [2] that did recommend pelvic LN EBRT. However, the overall benefit of EBRT in these two trials seems very similar, highlighting the possible controversies about the benefit of pelvic irradiation. In parallel, for intermediate and high-risk groups, according to D'Amico classification [5], prospective randomised trials that demonstrated the benefits of EBRT associated with hormone therapy versus EBRT alone included pelvic LN irradiation, because of a significant risk of microscopic invasion [6–11].

Three randomised studies on pelvic EBRT yielded controversial results [11–15]. The Radiation Therapy Oncology Group (RTOG) 77-06 trial randomised patients to prostate EBRT alone at a dose of 65 Gy or pelvic EBRT at 45 Gy followed by a boost to the prostate up to 65 Gy [14]. With a median follow-up of 12 years, this study showed no survival benefits in the pelvic radiation arm, in a population with a risk of LN invasion below 15% according to the Roach formula [16]. The GETUG (Groupe d'Etude des Tumeurs Urologiques et Génitales) 01 study investigated pelvic EBRT in 444 intermediate-risk patients and showed no difference in progression-free survival (PFS) or overall survival (OS) [13]. Similar to the RTOG 77-06 trial, half of the patients had a risk of LN involvement of less than 15%. The Clinical Target Volume (CTV) was a reduced pelvis (rising to S1–S2). The size of the radiation fields and the selected population could explain the lack of benefit in the pelvic EBRT arm. Finally, the RTOG 94-13 trial included 1323 patients with a risk of LN invasion above 15%, using a double randomisation on pelvic EBRT and timing of hormone therapy (neoadjuvant or concomitant and adjuvant). After a median follow-up of 7 years, no PFS benefits were found in the pelvic EBRT arm [12,15]. Post-stratification analyses suggested that patients with a risk of LN involvement below 15% and patients at high risk of extra-pelvic involvement did not benefit from pelvic EBRT. This study showed a favourable interaction between pelvic EBRT and neo-adjuvant hormone therapy, and an impact of the size of pelvic fields on biological recurrence-free survival [11].

The results of these phase III trials are consistent with data from retrospective studies [17,18]. Only patients with a risk of LN involvement above 15% and a low risk of extra-pelvic metastases could benefit from pelvic EBRT. This approximates patients with unfavourable intermediate risk or favourable high-risk prostate cancer [19].

Currently, three prospective randomised GETUG studies are assessing pelvic EBRT: GETUG 18 (NCT00967863), GETUG 22 (NCT01994239) and GETUG 21 (NCT01952223). The GETUG 21 trial includes patients with localised prostate cancer and two factors defining the high-risk group.

In order to conduct a conclusive and homogeneous assessment of the oncological effects and tolerance of pelvic EBRT in prostate cancer, cooperative groups must establish a CTV consensus for the delineation of LN considered at risk of involvement. The RTOG published such a consensus in 2009 [20] and the GETUG but also the UK CRUK PIVOTAL Group proposed CTV recommendations for pelvic EBRT as part of their prospective studies [21].

The aim of this review was to analyse recommendations from cooperative groups, and to comprehensively analyse published data on prostate cancer drainage, in order to discuss possible changes in the definition of LN areas of interest. We also present GETUG experts' opinions based on a survey on CTV LN definition in common practice, in order to identify the LN regions that could be omitted in pelvic radiation planning for prostate cancer.

Recommendations of cooperative groups on LN volumes defined for prostate cancer radiotherapy

In 2009, the RTOG published a consensus for LN contouring in pelvic radiotherapy for high-risk prostate cancer [20]. Based on bony anatomy, selected areas of interest were identified and contouring instructions were defined.

In the same period, during the development of the GETUG 18 study protocol, the GETUG experts did the same work and proposed contouring recommendations. Recently, the UK CRUK PIVOTAL Group [21] established guidelines including a detailed pelvic LN contouring atlas considering LN areas at risk. More specifically, this group proposed modifications to the RTOG technique, in order to reduce bowel and planning target volume overlap.

Despite some discrepancies, all those cooperative groups emphasise the necessity of a vascular outlining rather than a free hand definition of CTV. These recommendations defining LN areas of interest and CTVs are presented in Table1.

Literature review on prostate cancer LN drainage

Methods

We performed a literature search in July 2015 using the Medline database. We identified original and review articles addressing LN drainage, imaging and contouring of pelvic LN for prostate cancer. Abstracts written in any language other than English, editorials, case reports and letters were excluded. Keywords included prostate cancer, radiation therapy, lymphadenectomy, lymphography, sentinel lymph-nodes, magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), pelvic lymph-node dissection, drainage and recurrence. Titles were screened and studies were excluded if obviously irrelevant. Additional references were identified from other sources.

Data from publications on pelvic lymphography and anatomy texts

According to pelvic lymphography studies [22,23] and anatomy texts [24,25], the lymphatic drainage of the prostate essentially follows four different pathways:

- The lateral pathway along the inferior vesical vessels towards the internal iliac (formerly hypogastric) LN
- The posterior pathway along the rectum reaching the pre-sacral and promontory LN
- The inferior pathway along the pudendal axis towards the obturator fossa
- The pathway that goes from the base of the prostate towards the bifurcation of the common iliac artery to reach the external iliac LN.

From lymphographic studies, data are limited by the particle size of the contrast agent and the resolution of the technique. Although lymphography might underestimate the extent of LN involvement, it forms the basis of our knowledge of prostate drainage.

Data from LN dissection in surgical series and sentinel LN techniques

Some autopsy or radical prostatectomy series involving pelvic LN dissection reported the frequency of LN involvement [26–31]. Most frequently invaded areas are the obturator region (20–60%), the external iliac region (30–50%) and the internal iliac region (30–60%). The common iliac region (mainly the upper part) and the pre-sacral region are less commonly involved (<5–10%). In accordance with lymphographic data, preferential drainage pathways may vary depending on the location of the intra-prostatic tumour: base of the prostate, obturator fossa and below the external iliac vessels for posterior tumours, internal iliac, common iliac and pre-sacral areas for juxta-apical tumours, internal iliac axis for