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Review

CTV to PTV in cervical cancer: From static margins to adaptive radiotherapy

Du CTV au PTV dans les cancers du col utérin : vers une radiothérapie adaptative

R. Sun [a,*], R. Mazeron [a], C. Chargari [a], I. Barillot [b,c]

[a] *Radiation Oncology Department, Gustave-Roussy Cancer Campus, Paris-Sud University, 94805 Villejuif cedex, France*
[b] *Radiation Oncology Department, Bretonneau University Hospital, 37000 Tours, France*
[c] *François-Rabelais University, 37000 Tours, France*

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ABSTRACT

Intensity-modulated radiotherapy (IMRT) is increasingly used in order to minimize the gastrointestinal, genitourinary, and hematological toxicity in cervical and uterine cancers. However, the benefit of this high-precision approach is detracted by the margins applied to the clinical target volume (CTV) to generate the planning tumor volume (PTV), taking into account tumor and surrounding organs movements, deformations, and volume changes. Adequate PTV margins should be large enough to prevent geographical misses, but not excessive, which might end the benefit from IMRT. The objectives of this review were: (a) to present the evidence available for the determination of CTV-PTV margin for uterine cancers; (b) to highlight the impact of these margins in the context of adaptive radiotherapy; and (c) to discuss the role of the PTV concept in intracavitary brachytherapy.

Mots clés :
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RÉSUMÉ

La radiothérapie conformationnelle avec modulation d'intensité (RCMI) est de plus en plus utilisée dans les cancers du col et du corps de l'utérus, dans le but de minimiser la toxicité gastro-intestinale, génito-urinaire et hématologique. Cependant, le bénéfice de l'utilisation de cette technique de haute précision dépend des marges appliquées au volume cible antomoclinique (CTV) afin de construire le volume cible prévisionnel (PTV), nécessaires pour prendre en compte les mouvements de la tumeur et des organes voisins, ainsi que les déformations et modifications de volumes de ces organes. Les marges du volume cible prévisionnel doivent être assez larges pour éviter de manquer le volume cible, mais ne doivent pas être excessives, au risque de compromettre le bénéfice apporté par la modulation d'intensité. Les objectifs de cette mise au point étaient : (a) de présenter les données objectives pour la détermination du volume cible prévisionnel dans les cancers utérins ; (b) de mettre en évidence l'impact de ces marges dans le contexte de la radiothérapie adaptative ; et (c) de discuter du volume cible prévisionnel dans le cadre de la curiethérapie endocavitaire.

1. Introduction

If cervical cancer was the eleventh most common type of cancer in women (9.9 per 100,000 women) and the ninth most common cause of cancer mortality (3.3 per 100,000) in developed countries in 2012 [1], it was the second cause of cancer in developing countries in women with 444,500 new cases, and the third cause of death (230,200). Its treatment relies on the combination of pelvis ± paraortic EBRT and brachytherapy.

Intensity-modulated radiotherapy (IMRT) is increasingly used in order to minimize the gastrointestinal, genitourinary, and hematological toxicity [2–6,39]. Recent consensus guidelines defining the

* Corresponding author.
E-mail address: roger.sun@gustaveroussy.fr (R. Sun).

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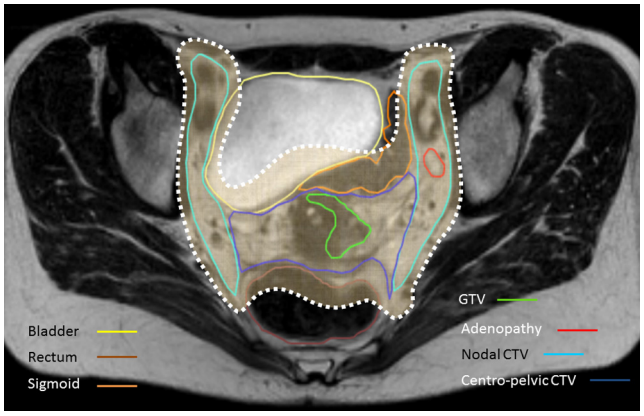

Fig. 1. Generation of a PTV from a CTV by applying directional margins of 7 mm around the nodal CTV; 20 mm anteriorly, 15 mm posteriorly around the centro-pelvic CTV. White dashes: PTV. Axial T2-MRI.

clinical target volume (CTV) for cervical cancer IMRT have been established. Lim et al. recommend that the CTV should include the gross tumor volume (GTV), entire cervix, entire uterus, parametria, ovaries and upper or even entire vagina depending on the vaginal involvement [7]. The nodal CTV includes pelvic nodes (common, internal and external iliac, obturator and presacral), and para-aortic nodes according to the work-up [7].

However, the benefit of this high-precision approach is detracted by the margins applied to the CTV to generate the planning tumor volume (PTV), taking into account tumor and surrounding organs movements, deformations, and volume changes [7–16]. Adequate PTV margins should be large enough to prevent geographical misses, but not excessive, which might end the benefit from IMRT (Fig. 1) [17]. For instance, Table 1 is depicting the findings of a meta-analysis showing that the dosimetric benefit of IMRT is finally less important than expected [18]. Modern image-guidance techniques allow reducing setup uncertainties, but also controlling the position of the CTV at each fraction. Redefining the optimal CTV-PTV margins is therefore crucial. The stake is high, as small variations in the margins imply important variation of volumes.

The objectives of this review are:

- to present the evidence available for the determination of CTV-PTV margin for uterine cancers (pelvic interfraction and intrafraction organ motion reported and actual guidelines);
- to highlight the impact of these margins in the context of adaptive radiotherapy;
- to discuss the role of the PTV concept in intracavitary brachytherapy.

2. Material and methods

A review of English and French literature available on Medline/PubMed (US National library of Medecine, Bethesda, USA) and Google Scholar (Google, Mountain View, USA) databases was performed using the following terms: uterine neoplasms, cervical cancer, target volume, organ motion, image-guided radiotherapy, and brachytherapy with controlled vocabulary and text word terms. We focused particularly on the CTV-PTV margin of cervical cancer, where the motion of uterus is a significant concern for the treatment planning, whereas radiotherapy for uterine corpus cancer take place essentially after hysterectomy [19].

Table 1
Dosimetric benefit of intensity-modulated radiotherapy compared to 3D radiotherapy for a prescription of 45 Gy in the pelvis.

	25 Gy	30 Gy	35 Gy	40 Gy	45 Gy
Rectum	NS	−26.4%	−27.0%	−37.3%	−39.5%
Small bowel	NS	NS	NS	−17.8%	−17.3%
Bladder	NS	NS	NS	NS	NS
Bone marrow	NS	NS	NS	NS	NS

According to Yang et al. [18].
NS: non-significant.

3. Uterus movements assessments

The CTV-PTV margin comprises the internal margin, related to organ motion, and the setup margins [20]. To define the required margins, studies were led to assess the uterine movements. A dozen of studies, focusing on interfraction movements, are available [16]. They are heterogeneous in terms of methodology and endpoints. Intrafractional movements have been less extensively investigated, but they seem to have less impact. For instance, Chan et al. concluded that the mean anteroposterior and cranio-caudal shifts during treatment were respectively 0.13 mm backward (range: −2.8 to 2.6 mm), 0.10 mm caudally (−6.4 to 10.9), with a mean rotation of −0.19° (−6.2 to 9.2) [10].

3.1. Movements of the cervix

Several studies specifically assessed the movements of the cervix [10,12,13,21–25]. Their methodology relied on the localization of the cervix using 3D-images (cone-beam, CT, or MRI), or fiducials markers and portal imaging. Motions were measured from the barycenter of the cervix or from its boundaries. In the overall, most of the studies showed that movements of the cervix are larger in the anteroposterior and superior-inferior direction than laterally. The mean interfractional movements amplitude ranged from 2.4 to 16 mm in the anterior-posterior, 1.5 to 8 mm in the superior-inferior and 0.3 to 10 mm in the lateral directions (Fig. 2) [16]. Studies using fiducials seemed to report smaller movements.

3.2. Movements of the uterine corpus

According to the studies summarized on Fig. 2, the movements of the uterine corpus seem larger than those of the cervix [10,11,26–29]. The mean reported movements ranged from 3.3 to 14.2 mm in the anterior-posterior, 6.1 to 9.5 mm in the superior-inferior, and 0.7 to 6.5 mm in the lateral direction.

3.3. Impact of bladder and rectum filling on the movements of the uterus

Some studies concluded that uterus movements are correlated to bladder filling (Fig. 3). However, the amplitude of the uterine displacements according to the bladder filling is extremely variable among the patients, ranging from negligible, up to 40 mm in the superior-inferior direction and 65 mm in the anterior-posterior direction [30]. For instance, an individual rotation of 91° of the uterus was reported, associated with an increased bladder repletion from 45 to 181 cm^3, leading to a shift of 48 mm in the anterior-posterior direction [27].

Overall, the uterine body shifts are wider in the anterior-posterior and superior-inferior directions, with larger movements of the fundus, lesser along the endocervical canal, and least at the os [30,31]. Chan et al. concluded that each 10-cm^3 decrease in bladder volume was associated to a shift of 18 mm and 8 mm caudally for the fundus and the endocervical canal respectively, and of 3 mm anteriorly for the cervix [10]. Huh et al. reported that 18% of patients had a greater than 30° variation in any angle, and suggested that patients aged < 60 years had more important movements [11].