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Review article

3D brachytherapy for cervical cancer: New optimization ways

Col utérin : curiethérapie tridimensionnelle et nouvelles voies d'optimisation dosimétrique

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ABSTRACT

Brachytherapy has known major improvements in recent decades. It represents an essential component of local treatment of cervix cancers. One major breakthrough was the advent of 3D imaging for image-guided brachytherapy. Doses could be prescribed to volumes. This allows better delineation and coverage of target volumes, as well as organs at risk (bladder, rectum, sigmoid) protection. Local recurrences have been consequently reduced and survival has been improved. In addition, improvement and development of new applicators have facilitated the delivery of interstitial treatments. Afterloading applicators, associated with 3D imaging, allow dosimetry optimization in order to improve the coverage of the target volumes (dose in 90% of the high risk clinical target volume) and to limit dose to the organs at risk. In the future, more personalized treatments will be achieved through more advanced applicators and/or by improving the accuracy of imaging at the time of brachytherapy.

Mots clés :
Curiethérapie guidée par l'image
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RÉSUMÉ

La curiethérapie a connu de grandes améliorations ces dernières décennies. C'est une technique essentielle du traitement local des cancers du col de l'utérus localisés. L'une des avancées majeures est l'avènement de l'imagerie tridimensionnelle permettant des curiethérapies guidées par l'image. Les doses peuvent maintenant être prescrites dans un volume. Cela permet une meilleure délimitation et couverture des volumes cibles, ainsi que l'épargne des organes à risque (vessie, rectum, sigmoïde). Grâce à cela, les récidives se sont raréfiées et la survie allongée. En outre, le perfectionnement et le développement de nouveaux applicateurs ont permis la réalisation de curiethérapie interstitielle lorsque celle-ci est nécessaire. Enfin, les applicateurs à chargement différé, associés à l'imagerie tridimensionnelle, permettent une optimisation de la dosimétrie pour améliorer la couverture des volumes cibles (dose rminimale couvrant 90 % [D90] du volume cible anatomoclinique à haut risque) et restreindre la dose reçue par les organes à risque. À l'avenir, des traitements encore plus personnalisés pourront être réalisés grâce à des applicateurs plus perfectionnés et/ou à une amélioration de la précision de l'imagerie au moment de la curiethérapie.

1. Introduction

Cervix cancer is the third most common cancer in women worldwide. In France, the limited vaccination coverage has little to no effect on its incidence [1].

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Standard treatment for locally advanced cervical cancers (FIGO IB2-IVa) consists of a combination of chemoradiation with external beam radiation therapy and uterovaginal brachytherapy [2]. Brachytherapy is an established and mandatory component of the treatment of cervical cancer, despite the decline in use observed in the last few years [3,4]. This decline was due partly to the new radiation delivery techniques (intensity-modulated and stereotactic body radiotherapy). Gill et al. showed that brachytherapy use was associated with an improved overall survival, as compared to modern external beam radiation therapy techniques for boost delivery [5]. Brachytherapy requires a specific practical training and has a long learning curve. These parameters may have contributed to the decrease of brachytherapy procedures. However, brachytherapy is still not an optional treatment and the recent evolutions in 3D imaging can be translated into this technique.

2. From 2D to 3D: image-guided adaptive brachytherapy

Afterloaders applicators and computer software enable the integration of 3D imaging into treatment planning and improve treatment accuracy. Historically 2D-brachytherapy delivery was planned with X-rays, with dose specified at points (point A) or surface isodose, but without real volume delineation. 3D brachytherapy allows an accurate delineation of target and organs at risk volumes. Nowadays, 3D based image-guided brachytherapy has increased worldwide. Computed tomography (CT) is the most commonly used imaging modality, because access to this equipment in radiation therapy department is easier than magnetic resonance imaging (MRI). Still, MRI is recommended [6–8]. MRI is more accurate than CT for target volumes. CT overestimates target volumes, inducing laterally larger delineated volumes, which could lead to higher organ at risk dosage and treatment toxicity [9].

2.1. Delineation

Brachytherapy allows very high dose at some precise points and volumes and very low dose to very close areas due to rapid fall-off. Minimal inaccuracies could have significant dosimetric impact on organs at risk and target coverage and quality of delineation is therefore a very important part of process [10]. Recommendations on delineation have been published in 2005 by GEC-ESTRO in order to homogenize practices [11,12]. Online delineation workshops have been shown to allow training of geographically dispersed physicians and delineation harmonization [13].

A joint report from ICRU and the GEC-ESTRO recommends to report as clinical target volumes at time of brachytherapy on T2-weighted MRI [14]:

- residual gross tumor volume as all remaining T2-bright areas;
- adaptive high-risk target volume as the entire cervix and any regions of high-to-intermediate signal intensity (grey zones) in parametria, uterus or vagina and any residual disease detected on clinical examination or imaging at brachytherapy time (residual gross tumor volume);
- intermediate risk target volume as areas of the initial pathologic tissue before any treatment superimposed on the topography at brachytherapy time and at least a margin of 0.5 to 1.5 cm around the adaptive high risk target volume, subtracting out the organs at risk;
- adaptive low risk target volume as areas at risk for potential spreading from the primary tumor. It includes whole parametria, whole uterus, upper part of the vaginal and anterior and posterior spaces towards bladder and rectum. This volume is defined at diagnostic for external beam radiation therapy.

Some recommendations are also given for organs at risk:

- bladder must be delineated as the whole bladder with outer bladder wall including bladder neck;
- rectum: outer rectal wall from the anal sphincter to transition into sigmoid;
- sigmoid: outer sigmoid wall from the rectosigmoid flexure to a least 2 cm above the parametria and uterus;
- bowel: outer contours of loops within 3 or 4 cm to the uterus and applicator.

2.2. Dose reporting

Dose reporting for target volumes should mention:

- TRAK;
- point A dose;
- minimal dose covering 98% of the target volume (D98), minimal dose covering 90% of the target volume (D90), minimal dose received by 50% of the target volume (D50) for adaptive high risk target volume;
- D98 and D90 for intermediate risk target volume if used for prescription;
- D98 for residual gross tumor volume;
- D98 for pathological lymph nodes if there are any.

For organs at risk, ICRU and GEC-ESTRO recommend to report doses to:

- rectovaginal reference point dose (previously ICRU rectal point);
- bladder reference point dose;
- minimum doses to the most exposed 2 cm^3 (D2 cm^3) and the minimum doses to the most exposed 0.1 cm^3 (D0.1 cm^3) of each organ at risk: rectum, bladder, sigmoid and bowel;
- minimum dose received by 98% of volume (D98%), minimum dose received by 50% of the volume (D50%), minimum dose received by 2% of the volume (D2%) as intermediate and low parameters;
- vaginal point doses at level of sources, lower and mid vagina doses defined as the point of the posterior inferior of the bone symphysis and posterior inferior of the bone symphysis (PIBS) $\pm$ 2 cm.

2.3. 3D imaging

The D90, D100 and percent of the volume receiving 100% of the prescription dose (V100) are maximized while reducing dose to organs at risk after MRI delineation. Regarding organs at risk, the two imaging techniques are almost equivalent [15]. For MRI imaging, multiplanar axial, coronal and sagittal T2-weighted acquisitions are required [16,17].

Adjunction of other imaging like diffusion-weighted MRI, dynamic contrast-enhanced MRI and fluorodeoxyglucose (FDG) positron emission tomography (PET) may precise tumor volumes and decrease delineation variability [18,19]. Mean apparent diffusion coefficient was shown to be an independent predictor of disease free-survival [20].

If CT imaging is used, iodine contrast allows to better distinguish the cervix from the uterus body [9]. In this case, MRI before brachytherapy application is preferable to adapt volumes. These approaches increased treatment complexity but improved efficacy [21].

Switching from radiographs to 3D imaging significantly reduced toxicity and also increased local control and survival.

In the EMBRACE study, a prospective observational trial, MRI was set as the gold-standard for image-guided brachytherapy planning. The objectives of this study were to introduce MRI-based brachytherapy in locally advanced cervical cancer in a multicentre