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Original article

What to expect from immediate salvage hysterectomy following concomitant chemoradiation and image-guided adaptive brachytherapy in locally advanced cervical cancer

Résultats de l'hystérectomie immédiate de rattrapage dans les cancers du col utérin localement évolués, après chimioradiothérapie et curiethérapie guidée par l'image

P. Castelnau-Marchand [a], C. Chargari [a], R. Bouaita [a], I. Dumas [b], G. Farha [a], L. Kamsu-Kom [a], E. Rivin del Campo [a], F. Martinetti [b], P. Morice [c], C. Haie-Meder [a], R. Mazeron [a,*]

[a] *Radiotherapy Department, Gustave-Roussy Cancer Campus, 114, rue Édouard-Vaillant, 94805 Villejuif cedex, France*
[b] *Medical Physics Department, Gustave-Roussy Cancer Campus, 114, rue Édouard-Vaillant, 94805 Villejuif cedex, France*
[c] *Gynaecological Surgery Department, Gustave-Roussy, Cancer Campus, 114, rue Édouard-Vaillant, 94805 Villejuif cedex, France*

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ABSTRACT

Purpose. – Concomitant chemoradiation followed by brachytherapy is the standard treatment for locally advanced cervical cancers. The place of adjuvant hysterectomy remains unclear but tends to be limited to incomplete responses to radiotherapy or local relapse. The aim was to analyse the benefit from immediate salvage surgery following radiation therapy in incomplete responders.
Methods. – Among the patients with locally advanced cervical cancer treated with concomitant chemoradiation followed by 3D image-guided adaptive brachytherapy and hysterectomy, cases with genuine macroscopic remnant, defined as at least 1 cm in width, were identified. Their clinical data and outcomes were retrospectively reviewed and compared to the patients treated with the same modalities.
Results. – Fifty-eight patients were included, with a median follow-up of 4.2 years. After hysterectomy, 9 patients had macroscopic residual disease, 10 microscopic and the remaining 39 patients were considered in complete histological response. The 4-year overall survival and disease-free survival rates were significantly decreased in patients with macroscopic residual disease: 50 and 51% versus 92% and 93%, respectively. Intestinal grades 3–4 toxicities were reported in 10.4% and urinary grades 3–4 in 8.6% in the whole population without distinctive histological features. Planning aims were reached in only one patient with macroscopic residuum (11.1%). In univariate analysis, overall treatment time (> 55 days) and histological subtype (adenocarcinomas or adenosquamous carcinomas) appeared to be significant predictive factors for macroscopic remnant after treatment completion ($P = 0.021$ and $P = 0.017$, respectively). In multivariate analysis, treatment time was the only independent factor ($P = 0.046$, odds ratio = 7.0).
Conclusions. – Although immediate salvage hysterectomy in incomplete responders provided a 4-year disease-free survival of 51%, its impact on late morbidity is significant. Efforts should focus on respect of treatment time and dose escalation. Adenocarcinoma might require higher high-risk clinical target volume planning aims.

Mots clés :
Chimioradiothérapie concomitante
Curiethérapie adaptative guidée par l'image
Cancer du col utérin localement avancé
Hystérectomie
Maladie résiduelle

RÉSUMÉ

Objectif de l'étude. – La chimioradiothérapie concomitante suivie de curiethérapie utérovaginale est le traitement standard des cancers du col utérin localement évolués. La place de l'hystérectomie adjuvante reste incertaine mais tend à se limiter aux réponses incomplètes et aux rechutes locales. L'objectif de l'étude était d'analyser le bénéfice de la chirurgie de rattrapage immédiate après radiothérapie.

* Corresponding author.
E-mail address: renaud.mazeron@gustaveroussy.fr (R. Mazeron).

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Méthodes. – Parmi les patientes atteintes de cancer du col utérin localement évolué dont le traitement a été une chimioradiothérapie suivie de curiethérapie adaptative guidée par l'image et hystérectomie, les cas avec résidu postopératoire macroscopique, défini comme au moins 1 cm de grand axe, ont été identifiés. Leurs données ont été revues rétrospectivement et comparées à celles des patientes traitées selon les mêmes modalités.
Résultats. – Cinquante-huit patientes ont été incluses, avec un suivi médian de 4,2 ans. Après hystérectomie, neuf patientes étaient atteintes d'une maladie résiduelle macroscopique, dix microscopique, et les 39 autres étaient en situation de réponse histologique complète. Les probabilités de survie globale et de survie sans récidive à 4 ans étaient significativement plus faibles en cas de résidu macroscopique : respectivement 50 et 51 % contre 92 et 93 %. Une toxicité intestinale de grades 3–4 a été rapportée dans 10,4 %, et urinaire dans 8,6 %, dans l'ensemble de la population, sans distinction en fonction du groupe de réponse. Les objectifs de planification n'ont été atteints que pour une seule patiente, chez qui a été mis en évidence un résidu macroscopique (11,1 %). En analyse unifactorielle, l'étalement du traitement (plus de 55 jours) et le sous-type histologique (adénocarcinomes et carcinomes adénosquameux) semblaient être des facteurs prédictifs significatifs d'un résidu macroscopique ($p = 0{,}021$ et $p = 0{,}017$, respectivement). En analyse multifactorielle, l'étalement était le seul facteur indépendant ($p = 0{,}046$, *odds ratio* = 7,0).
Conclusion. – Bien que l'hystérectomie immédiate de rattrapage ait permis d'obtenir une probabilité de survie sans rechute de 51 % à 4 ans, son impact sur la morbidité tardive est significatif, et les efforts doivent se concentrer sur l'optimisation des plans de traitement et le respect de l'étalement. Les adénocarcinomes pourraient requérir des objectifs de planification plus élevés.

1. Introduction

Definitive radiation therapy has been considered as the standard management in locally advanced cervical cancers for years [1]. However, in some countries, postradiation hysterectomy has been considered helpful to safeguard the local control in stage IB and II cervical cancers. This strategy has stirred controversy over the years due to the lack of evidence showing its benefits, although retrospective studies suggesting that postradiation surgery might be interesting to achieve local control after chemoradiotherapy have been reported.

Two major advances occurred in the treatment of locally advanced cervical cancers during the last decade, which both improved the efficiency of radiotherapy and clearly questioned the need for adjuvant hysterectomy. The first was concomitant chemotherapy which showed an improvement of local, regional and distant control rates, especially for stage I and II diseases [2]. The second was the emergence of 3D image-guided adaptive brachytherapy allowing doses escalation while preserving the organs at risk [3]. Recent monocentric studies reported promising results in terms of local control rates and morbidity [4–6]. In most institutions, postradiation hysterectomy is nowadays limited to incomplete responders to radiotherapy or local relapses. A few years ago, Azria et al. have even challenged this role as they reported poor outcomes and high distant metastasis rates in patients with histologically proven bulky residual disease [7]. The aim of this study was to report the outcomes and morbidity of patients that underwent salvage hysterectomy after the best current treatment modalities: chemoradiotherapy followed by 3D image-guided adaptive brachytherapy. To circumvent the problems posed by the selection of patients who may benefit from hysterectomy, patients with genuine residual disease, based on pathological findings, were selected. Secondly, their characteristics were compared to a control group of patients whose disease was in complete response after the same treatment.

2. Materials and methods

2.1. Patients

As part of a retrospective study, patients with histologically proven cervical carcinoma (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma) were selected from the database of our institution. Inclusion criteria comprised patients with stage IB1 N+ to IVA tumours, according to the International Federation of Gynecology and Obstetrics (FIGO) classification, who underwent chemoradiotherapy followed by 3D image-guided adaptive brachytherapy and adjuvant hysterectomy. Those with residual disease considered significant in case of remnant > 1 cm in width, and therefore as an improper response to radiotherapy were selected. The remaining patients were used as controls for comparison. Patients had to have undergone hysterectomy as part of the initial strategy to be eligible. In the early 2000, at our institution, systematic postradiation hysterectomy was offered in stage I-II lesions. After the completion of the randomized GYNECO 02 study in 2006, postradiation hysterectomy was abandoned unless in case of proven residual disease [8]. Some patients who were referred later from other institutions for treatment with a planned postradiation hysterectomy were included.

2.2. External beam radiation therapy

All patients were initially treated by pelvic with or without para-aortic conformal external beam radiation therapy, with high-energy photons (18–20 MeV), and a standard fractionation (45 Gy in 25 fractions of 1.8 Gy). Concomitant chemotherapy was systematically added when not refused or contraindicated, in most cases cisplatinium 40 mg/m^2 weekly. Treatment planning was based on a CT-scan, with 3 mm thick axial slices. An intravenous iodine injection was performed whenever possible to enhance the cervix and the lymph nodes. The pelvic clinical target volume (CTV) contained the cervix, the whole uterus, the parametria and a part of the vagina depending on its invasion. The lymph nodes CTV encompassed the external and internal iliac areas, ilia-obturator, presacral and common iliac nodes. All of these structures were delineated on an IsoGray® platform (DOSIsoft SA, Cachan, France) [9]. Two planning target volumes (PTV) were generated by applying automatically 3D margins of 7 mm around the lymph nodes CTV and at least 10 mm around the pelvic CTV depending on the repletion of the rectum and of the bladder. A four-field box ballistic was used, and the leaves were automatically placed around the PTV to ensure its perfect coverage.