Cancer/Radiothérapie 18 (2014) 524–534

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Review article

Salvage reirradiation for locoregional failure after radiation therapy for prostate cancer: Who, when, where and how?

Modalités des réirradiations de rattrapage pour les rechutes locales des cancers de la prostate

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ARTICLE INFO

Keywords:
Prostate cancer
Local failure
Oligometastases
Salvage radiotherapy
Salvage brachytherapy de rattrapage

ABSTRACT

Even in the current era of dose-escalated radiotherapy for prostate cancer, biochemical recurrence is not uncommon. Furthermore, biochemical failure is not specific to the site of recurrence. One of the major challenges in the management of prostate cancer patients with biochemical failure after radiotherapy is the early discrimination between those with locoregional recurrence only and those with metastatic disease. While the latter are generally considered incurable, patients with locoregional disease may benefit from emerging treatment options. Ultimately, the objective of salvage therapy is to control disease while ensuring minimal collateral damage, thereby optimizing both cancer and toxicity outcomes. Advances in functional imaging, including multiparametric prostate MRI, abdominopelvic lymphangio-MRI, sentinel node SPECT-CT and/or whole-body PET/CT have paved the way for salvage radiotherapy in patients with local recurrence, microscopic nodal disease limited to the pelvis or oligometastatic disease. These patients may be considered for salvage reirradiation using different techniques: prostate low-dose or high-dose rate brachytherapy, pelvic and/or lomboaortic image-guided radiotherapy with elective nodal irradiation, focal nodal or bone stereotactic body radiation therapy (SBRT). An individualized approach is recommended. The decision about which treatment, if any, to use will be based on the initial characteristics of the disease, relapse patterns and the natural history of the rising prostate specific antigen (PSA). Preliminary results suggest that more than 50% of patients who have undergone salvage reirradiation are biochemically relapse-free with very low rates of severe toxicity. Large prospective studies with a longer follow-up are needed to confirm the promising benefit/risk ratio observed with salvage brachytherapy and or salvage nodal radiotherapy and/or bone oligometastatic SBRT when compared with life-long palliative hormones.

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http://dx.doi.org/10.1016/j.canrad.2014.07.153
1278-3218/

Mots clés :
Cancer de prostate
Rechute locale
Oligométastases
Radiothérapie de rattrapage
Curiethérapie de rattrapage

RÉSUMÉ

Une rechute biochimique n'est pas si rare après radiothérapie d'un cancer de prostate, même à l'heure actuelle de la radiothérapie avec escalade de dose. Par ailleurs, une rechute biochimique n'est pas spécifique d'un site de rechute. Un des enjeux majeur de la prise en charge d'une rechute biochimique après radiothérapie d'un cancer de la prostate est la différenciation précoce possible entre une rechute locorégionale et une rechute métastatique. Bien que les rechutes métastatiques soient considérées comme incurables, les patients atteints d'une maladie locorégionale peuvent bénéficier d'options thérapeutiques émergentes. L'objectif ultime d'un traitement de rattrapage est de contrôler la maladie tout en assurant un minimum de dommages collatéraux, ce qui permet d'optimiser à la fois les résultats carcinologiques et les séquelles. Les avancées en imagerie fonctionnelle, incluant l'IRM de prostate multiparamétrique, la lymphangio-IRM utilisant des nanoparticules d'oxydes de fer, la technique du ganglion sentinelle en SPECT (*single photon emission tomography*)/scanographie et/ou la tomographie par émission de positons (TEP) du corps entier couplée à la scanographie ont ouvert la porte à de nouvelles possibilités de radiothérapie de rattrapage chez les patients en situation de rechute locale, d'un envahissement ganglionnaire microscopique limité au pelvis ou d'une maladie oligométastatique. Une réirradiation peut être proposée à ces patients grâce aux différentes techniques : une curiethérapie prostatique de bas ou de haut débit de dose, une irradiation ganglionnaire prophylactique pelvienne et/ou lomboaortique avec modulation d'intensité guidée par l'image, une radiothérapie stéréotaxique focalisée sur une rechute ganglionnaire ou osseuse isolée. Une approche individualisée est recommandée. Le choix du traitement de rattrapage qui peut être délivré repose sur les caractéristiques initiales de la maladie, la connaissance des sites de rechute et l'histoire naturelle du cancer de prostate en situation de rechute biochimique. L'analyse des résultats préliminaires suggère que plus de la moitié des cancers ayant été de nouveau irradiés seraient contrôlés biochimiquement avec des taux faibles de toxicité sévère. De larges études prospectives avec un recul plus long sont nécessaires pour confirmer cet indice thérapeutique prometteur observé avec la curiethérapie de rattrapage et/ou la radiothérapie ganglionnaire de rattrapage et/ou la radiothérapie stéréotaxique osseuse par comparaison à un traitement hormonal palliatif donné à vie.

1. Introduction

Multiple randomized trials have demonstrated that dose-escalated radiotherapy improves biochemical control [1–4]. However, biochemical failure still occurs in 20 to 30% of patients. Furthermore, in a study by Zelefsky et al., post-treatment biopsies showed that 15 to 20% of patients treated with dose-escalated radiotherapy have residual disease, suggesting at least local failure [5]. While a rising prostate specific antigen (PSA) level suggests recurrent disease, it is not specific to the location of the recurrence, and may reflect locoregional relapse and/or distant metastases. Currently, the standard management of patients with PSA failure is to restage them thanks to a CT, MRI and bone scan. However, the accurate detection of micrometastases so as to avoid futile salvage therapy remains challenging.

Emerging functional imaging techniques, such as multiparametric magnetic resonance imaging (MRI) of the prostate after radiotherapy to identify local recurrence [6], ^{11}C- or (^{18}F)-fluorocholine positron emission tomography (PET) combined with computed tomography (chol-PET/CT) and MR lymphangiography with ferumoxtran [7] to detect occult local and/or regional and or/bone oligometastases have shown promising results. The earlier and more accurate characterization of disease foci has provided opportunities for salvage treatments, such as stereotactic body radiation therapy (SBRT) or brachytherapy, in patients with oligometastases. To further support salvage therapy for those with locoregional recurrence, Coen et al. reported that distant failures at 10 years and time to distant failure are associated with local control [8].

Although locally advanced primary prostate cancer and biochemical failure have a worse prognosis, cancer-specific survival rates remain very high when compared with other cancers. In patients with locally advanced prostate cancer (i.e. PSA 50–100, M0–Mx), cancer-related death rates at 10 years were 10% in the case of a curative treatment vs. 36% with a palliative strategy [9]. In the case of locally advanced disease at diagnosis, it is now established that prostate radiation therapy also improves overall survival [10,11].

Because of the protracted natural history of prostate cancer, even after biochemical failure, the impact of salvage therapies on patients' quality of life should be considered. Indeed, expectant management can also be an option. This is based on life expectancy data from a randomized trial, which demonstrated that men over 76 years of age with comorbidities and a PSA doubling time of over 2 years should not be considered for salvage treatments [12]. Similarly, patients who have previously received high integral doses to large volumes of critical structures such as the bowel, bladder or rectum for their prostate cancer may not be ideal candidates for additional salvage radiotherapy. Thus, patients with biochemical failure after previous radiotherapy for prostate cancer can present in a myriad of ways, and as such, an individualized approach that takes into account factors related to the patient, the treatment and the disease is recommended.

In this review, we will discuss new investigational salvage radiation strategies for patients with local recurrence after external beam radiotherapy or for those with oligometastatic relapse affecting the nodes and/or bones. Recommendations are given on the selection of patients and the techniques most suitable for each situation (small volume failure inside or outside the previously irradiated volume).

2. Patterns of local failures after radiation

In the study by Zelefsky et al., even with dose-escalated external beam radiotherapy, 15–20% of patients have a positive post-treatment biopsy, confirming local failure [5]. In a large prostate cancer registry of 5277 men initially treated with radical prostatectomy or external beam radiotherapy, patients with recurrent disease were more likely to have bone metastases (15% vs. 1%, $P < 0.01$), higher prostate cancer-specific mortality (45% vs. 0%, $P < 0.01$) and overall deaths (19% vs. 3%, $P < 0.01$) than those who did not recur [13].

Among patients who have salvage therapy, only 7% die whereas 25% die if there is no salvage [13]. Before the advent of modern