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Overview

Re-irradiation in Gynaecological Malignancies: A Review

A.H. Sadozye

Beatson West of Scotland Cancer Centre, Gartnavel General Hospital, Glasgow, UK

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Abstract

Re-irradiation in gynaecological malignancies has become an increasingly frequent consideration. This can be delivered in multiple settings, with the most common being a patient with a history of cervical cancer developing a new vaginal cancer or endometrial cancer with local recurrence after hysterectomy and adjuvant pelvic radiation. A systematic review of the literature has unearthed a handful of reports, most delivering brachytherapy, with a small number on both external beam radiotherapy and stereotactic ablative radiotherapy. A detailed review of these papers suggests that it is not possible to draw any firm conclusions or put forward guidelines for this challenging area of gynaecological oncology. Here the author has provided a brief account of each paper, followed by a discussion of the literature, aiming to outline some very broad principles for management. It is recommended that such patients be referred to centres that treat high volumes of gynaecological malignancies, as the experience of the treating oncologist may be the most important factor in the management of these patients.

Key words: Brachytherapy; interstitial brachytherapy; re-irradiation; SABR; stereotactic ablative radiotherapy

Statement of Search Strategies Used and Sources of Information

Medline, Embase, Central and Cochrane databases were searched for English-language articles on the topic of re-irradiation in pelvic/gynaecological malignancies. The initial search revealed 57 articles, which, after deduplication, were reduced to 36. After further review, the articles were restricted to 29.

Introduction

Over the past few decades, improvements in the treatment of gynaecological malignancies have resulted in an increasing number of survivors and, hence, an increase in second malignancies of the gynaecological tract. The most common example of this is a patient who has had radiotherapy or chemoradiotherapy for cervical cancer, presenting years later with a new vaginal cancer. As such, over the last two decades, there has been an increasing indication for re-irradiation. There is much uncertainty and anxiety regarding re-irradiation and what complications one should anticipate and warn our patients about. This overview aims to review appropriate publications and explore the possibility of suggesting some recommendations.

Materials and Methods

Medline, Embase, Central and Cochrane databases were searched for English-language articles on the topic of re-irradiation in pelvic/gynaecological malignancies. The initial search revealed 57 articles, which, after deduplication, were reduced to 36. After further review, the articles were restricted to 29.

Results

We were able to source 21 full-text articles. The rest were not accessible, even after contacting the British library.

Re-irradiation was carried out using the following three modalities:

Author for correspondence: Beatson West of Scotland Cancer Centre, Gartnavel General Hospital, Glasgow G12 0YN, UK. Tel: +44-141-301-7066.
E-mail address: azmat.sadozye@ggc.scot.nhs.uk.

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(i) conventional external beam radiotherapy (EBRT);
(ii) stereotactic ablative radiotherapy (SABR);

(iii) high dose rate (HDR) brachytherapy.

Conventional External Beam Radiotherapy

The first paper reported is from Prasasvinichai *et al.* [1] published in 1978. They reviewed their records from 1960 to 1970 and found 68 patients who had been aggressively retreated after initial treatment for cervical cancer. Of these, 40 patients had re-irradiation, either with brachytherapy or EBRT and brachytherapy. There is no information in this paper on the technique or dose and fractionation. However, the authors mentioned that there was a 37% late complication rate, mainly grade 3–4, with some patients experiencing more than one severe toxicity. The 5 year survival in this group was reported as 17.6%.

Prempree *et al.* [2] reported 10 cases who had recurrent cervical cancer after initial radical radiotherapy. The EBRT techniques described in this paper are not currently in use. Some patients only had EBRT, whereas the majority had EBRT and vaginal brachytherapy (VBT). The exact doses were not reported, but the authors provided a range between 55 and 78 Gy, presumably EQD2 to point 'A'. The authors described only one patient experiencing rectovaginal and vesicovaginal fistulae. They reported 70% long-term disease-free survival.

Wang *et al.* [3] reported 73 cases of late vaginal malignancy (either primary or recurrence) after initial treatment for cervical cancer, between 1972 and 1992. All of these patients were re-irradiated with curative intent using cobalt beam or 6 MV linear accelerator-based EBRT followed by VBT using either radium or cobalt after-loaders. External beam doses ranged from 45 to 50 Gy in 30–32 fractions in some patients (using a midline block after 25–30 Gy) followed by VBT using radium to a point 'A' dose of 60–72 Gy. Survival at 5 years was 40%. Late complications were reported in nearly half the patients, with nearly 25% severe bowel and bladder toxicity and 25% 'radionecrosis'.

Stereotactic Ablative Radiotherapy

Stereotactic radiotherapy is delivered either using Gamma Knife or linear accelerators. The main difference between intensity-modulated radiotherapy and SABR is the ability to deliver very high doses to an area of interest with a rapid fall off in dose, hence a much better dose profile to organs at risk. The nature of this mode of delivery is such that the volume of irradiation needs to be small; most would argue that the largest size is probably 3–5 cm.

SABR has found favour in some areas of the body, such as lung, where for small, peripheral T1–2 lesions it is now the standard of care. In some other tumours, such as prostate, it has been shown to be feasible and safe and randomised trials are ongoing to establish its role.

There has also been uptake for treating oligometastatic disease and recurrent tumours in various parts of the body, as is evident by multiple reports in the literature. Trials such as COMET, CORE and SAURON are ongoing in this area and will inform future decision making.

In the context of gynaecological cancers, SABR has three potential indications:

(i) central recurrences after radiotherapy;
(ii) isolated nodal metastasis;

(iii) boost to central disease when brachytherapy is not feasible.

Deodato *et al.* [4] treated 11 patients (12 lesions) with SABR using doses up to 30 Gy/six fractions treated daily. Of these, over half the patients had recurrent disease, having been treated previously with EBRT; 2 year disease-free survival was quoted at 81%. No grade 3–4 toxicity was reported.

Dewas *et al.* [5] reported a series of 16 patients with a variety of pelvic malignancies, recurrent to pelvic sidewall. These patients were treated with Cyberknife image-guided radiotherapy (SABR) to a dose of 36 Gy in six fractions over 3 weeks. They reported an actuarial local control rate of 51% at 1 year, with a median disease-free survival of 8.3 months. The treatment was very well tolerated, with no grade 3 toxicity reported after a median follow-up of more than 10 months.

Abusaris *et al.* [6] treated 33 patients with recurrent disease, post-radiotherapy, with SABR using Gamma Knife; the median dose of radiotherapy was 34 Gy, range 8–60 over one to 10 fractions.

They reported no grade 3 or higher toxicity; local control for the whole group at 2 years was 53%. Those who received EQD2 $>$ 60 Gy had a 100% local control at 2 years.

Pontoriero *et al.* [7] reported five patients re-irradiated with Cyberknife. The dose was 15–20 Gy/three to four fractions depending on organ at risk constraints. No grade 3–4 toxicity was reported up to 90 days after treatment. All patients had a radiological response to SABR.

Brachytherapy

Brachytherapy delivers high doses of radiation to tumour with a rapid fall off in dose, therefore minimising the dose to organs at risk. Because of this, it is an ideal modality for re-irradiation, provided the tumour is central and accessible.

Brachytherapy can either be interstitial or intracavitary. Interstitial brachytherapy can be either low dose rate (LDR) or HDR. The mode of delivery can be either needles (HDR or LDR) or using I123 seeds (LDR).

Intracavitary brachytherapy can be delivered using one of the following applicators, depending on the clinical situation:

(i) vaginal cylinders (segmented or un-segmented);
(ii) colpostats or ovoids only;

(iii) Fletchers set;

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