Clinical Oncology 26 (2014) 185–196

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

A Systematic Review of Organ Motion and Image-guided Strategies in External Beam Radiotherapy for Cervical Cancer

R. Jadon [*1], C.A. Pembroke [*1], C.L. Hanna [*], N. Palaniappan [*], M. Evans [*], A.E. Cleves [†], J. Staffurth [*‡]

[*] *Department of Clinical Oncology, Velindre Cancer Centre, Cardiff, UK*
[†] *Cancer Research Wales Library, Information Services, Velindre Cancer Centre, Cardiff, UK*
[‡] *School of Medicine, Institute of Cancer and Genetics, Cardiff University, Velindre Cancer Centre, Cardiff, UK*

Received 16 August 2013; received in revised form 18 November 2013; accepted 19 November 2013

Abstract

Advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), may significantly benefit cervical cancer patients, in terms of reducing late toxicity and potentiating dose escalation. Given the steep dose gradients around the planning target volume (PTV) with IMRT planning, internal movement of organs during treatment may cause geographical miss of the target and unnecessary organs at risk (OAR) inclusion into high dose regions. It is therefore important to consider the extent and patterns of organ motion and to investigate potential image-guided radiotherapy (IGRT) solutions before implementing IMRT for cervical cancer. A systematic literature search was carried out using Medline, Embase, Cochrane Library, Web of Science, Cinahl and Pubmed. Database-appropriate search strategies were developed based upon terms for uterine neoplasms, IGRT, organ motion and target volume. In total, 448 studies were identified and screened to find 39 relevant studies, 12 of which were abstracts. These studies show that within the target volume for cervical cancer radiotherapy, uterine motion is greater than cervical. Uterine motion is predominantly influenced by bladder filling, cervical motion by rectal filling. Organ motion patterns are patient specific, with some having very little (5 mm) and others having much larger shifts (40 mm) of the target volume. Population-based clinical target volume (CTV)–PTV margins would be large (up to 4 cm around the uterus), resulting in unnecessary OAR inclusion within the PTV, reducing the benefits of IMRT. Potential solutions include anisotropic margins with increased margins in the anteroposterior and superoinferior directions, or greater PTV margins around the uterine fundus than the cervix. As pelvic organ motion seems to be patient specific, individualised PTV margins and adaptive IGRT strategies have also been recommended to ensure target volume coverage while increasing OAR sparing. Although these strategies are promising, they need significant validation before they can be adopted into clinical practice.

Key words: Cervical cancer; external beam radiotherapy; IGRT; image guidance; IMRT; organ motion

Statement of Search Strategies Used and Sources of Information

Searches were carried out using Medline, premedline, Embase, Cochrane Library, Web of Science and CINAHL; no date or language restrictions were applied. Update searches were carried out in February 2013 and included an additional Pubmed search for e-publications ahead of print. Hand searches of reference lists were also undertaken. Peer-reviewed papers and conference abstracts were sought. Database-appropriate strategies were developed around the terms for uterine neoplasms, image-guided radiotherapy, organ motion and target volume using controlled vocabulary and text word terms.

Introduction

Cervical cancer is the third most common female cancer worldwide, with 60% of patients being diagnosed under the age of 50 years. Most patients have locally advanced disease where the standard treatment is chemoradiation followed by brachytherapy, with expected cure rates of 30–90% depending on stage [1]. Pelvic chemoradiation is associated

Author for correspondence: R. Jadon, Velindre Cancer Centre, Velindre Road, Whitchurch, Cardiff CF14 2TL, UK. Tel: +44-7980-846647; Fax: +44-2920-426036.

E-mail address: rashmi.jadon@wales.nhs.uk (R. Jadon).

[1] Contributed equally to the paper.

0936-6555/$36.00 © 2014 Published by Elsevier Ltd on behalf of The Royal College of Radiologists.
http://dx.doi.org/10.1016/j.clon.2013.11.031

with severe (grade 3–4) gastrointestinal and genitourinary late toxicity rates of 6–23% [2], often leaving young patients with distressing lifelong symptoms, including malabsorption, incontinence and fistulae.

Intensity-modulated Radiotherapy for Cervical Cancer

Recent years have seen the emergence of intensity-modulated radiotherapy (IMRT) for cervical cancer, which enables highly conformal dose delivery to target volumes (cervix, uterus, parametrium and pelvic lymph nodes) with a reduced dose to organs at risk (OAR) (bowel, rectum, bladder) [3–6].

Dosimetric reports show significantly reduced doses to bowel, rectum, bladder and bone marrow with IMRT for cervical cancer compared with traditional planning approaches [7–9]. Arc therapies, such as volumetric arc therapy and RapidArc, improve OAR sparing further, with the added benefit of a shorter treatment delivery time [10,11].

Early clinical data suggest that these dosimetric observations translate to less toxicity for patients [3,6,12]. A retrospective study showed reduced late gastrointestinal toxicity from 50% to 11% (all grades) [4]. Furthermore, IMRT may potentially allow dose escalation, as well as incorporation of 'boosts' to high risk areas to improve tumour control and survival.

The Problem of Organ Motion

Pelvic organs are naturally prone to positional and volumetric changes over time. As a result, the pelvic anatomy at the time of radiotherapy planning may differ from the pelvic anatomy during treatment. These individual organ changes may result in variations in the clinical target volume (CTV) position and shape.

When conventional 'box' radiotherapy techniques are used, the irradiated volume encompasses the whole pelvis from the sacral promontory to the obturator foramen. Internal organ motion is thus less important because the CTV is more likely to remain within the irradiated volume. The complex dose distributions achieved with IMRT, with concavities and relatively steep dose gradients, mean that the potential impact of internal organ motion needs to be revisited to avoid geographical miss.

The successful implementation of IMRT relies on accurate delineation of the CTV and selection of an appropriate margin around the CTV to form the planning target volume (PTV). Consensus outlining guidelines for cervical cancer IMRT recommend that the CTV should comprise the gross tumour volume (GTV), cervix, uterus, upper vagina, parametrium and pelvic nodes (obturator, common, internal and external iliac) [13]. The CTV–PTV margin has two components: the internal margin, which accounts for organ motion, and the set-up margin, which accounts for patient set-up and delivery errors [14].

Knowledge of organ motion within the CTV and the influences of adjacent organ filling (bladder, rectum, bowel) is required to determine an appropriate internal target volume (ITV). Margins should be evidenced based, ideally, utilising data from the treating institution. They should be large enough to minimise/prevent geographical miss, yet not too large or the clinical advantages of IMRT will be minimised [15].

Image-guided radiotherapy (IGRT), with its many aspects, including patient set-up, preparation, margin use and on-treatment imaging, aims to reduce geometric uncertainty. At a time when IMRT for cervical cancer is being adopted, the most reproducible and clinically practical IGRT methods must be determined.

Aims

The aims of this review are to evaluate external beam radiotherapy and the patterns and extent of pelvic interfraction and intrafraction organ motion reported for cervical cancer. Correlations of motion with bladder and rectal filling and IGRT solutions are reviewed.

Materials and Methods

Information Sources and Search Strategy

Searches were carried out using Medline, premedline, Embase, Cochrane Library, Web of Science and CINAHL; no date or language restrictions were applied. Update searches were carried out in February 2013 and included an additional Pubmed search for e-publications ahead of print. Hand searches of reference lists were also undertaken. Peer-reviewed papers and conference abstracts were sought. Database-appropriate strategies were developed around the terms for uterine neoplasms, image-guided radiotherapy, organ motion and target volume using controlled vocabulary and text word terms.

Eligibility Criteria

English and French language studies examining interfractional and intrafractional organ motion and IGRT techniques during external beam radiotherapy for definitive cervical cancer treatment were included. With the focus being on IMRT, brachytherapy studies were excluded. Postoperative cervical and endometrial cancer studies were excluded due to differing anatomies.

The quality and eligibility of the studies were assessed using three criteria: (i) Was the spectrum of patients included representative of those in clinical practice? (ii) Were the methods described in sufficient detail to permit replication of the study? (iii) Were the outcomes measured appropriate to the aims of the study?

Initial abstracts were screened for relevance by two authors (RJ, CAP), followed by assessment for eligibility of full-length articles.

Results

Outcomes of the systematic search are illustrated in Figure 1. Overall, 39 relevant studies (12 of which were