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Current Issues in Cervical Cancer Radiotherapy

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Cervical Cancer Radiotherapy

Cervical cancer is a significant global health burden being the 4th most common cause of cancer related death in women worldwide [1]. This is despite the introduction of primary and secondary prevention measures within the developed world. A high proportion of patients present with locally advanced disease, defined as FIGO stage 1B2 to IVA. In this group of patients the standard of care is to treat curatively with a combination of chemotherapy and radiation therapy using external beam therapy and brachytherapy. This leads to 5 year survival rates in the United Kingdom of 61% for FIGO stage IIB and 44% for FIGO stage IIIB [2]. Chemo-radiation can lead to significant morbidity due to dose delivered to the surrounding healthy organs at risk (OARs). 18%, 45% and 53% of patients experience low grade genitourinary, gastrointestinal and haematological toxicity respectively with 1.5%, 8% and 28% experiencing grade 3 or 4 genitourinary, gastrointestinal and haematological toxicity respectively. Late complications are less well documented and range from 5-25% of patients [3]. Cervical cancer can affect women at a young age and therefore minimisation of toxicity is vital.

New radiation techniques are becoming more widely available which aim to improve the therapeutic ratio by reducing OAR dose. Intensity Modulated Radiotherapy (IMRT) and image guided brachytherapy (IGBT) are two recent advances which have been incorporated into standard practice for cervical cancer in many countries.

IMRT is a radiation technique that enables dose to conform tightly to target volumes thereby increasing normal tissue sparing. It uses numerous beam segments and modulated beam intensity (or fluence) to deliver steep dose gradients and shapes, such as concave, that would otherwise be unachievable. In the treatment of gynaecological cancers this facilitates reductions of high doses to bladder, rectum, bone marrow and small bowel [4,5] which translates into reduced acute and chronic bowel and urinary toxicity; grade 3 diarrhoea 5.6% from 30.6% , acute gastrointestinal toxicity 53% from 95%, chronic gastrointestinal toxicity 11% from 50%, acute genitourinary toxicity 7% from 16% [6-8]. However, the safe delivery of IMRT relies upon accurate target volume delineation and a good understanding of target movement within the pelvis.

A clinical target volume (CTV) is delineated during the radiation therapy planning process to determine where dose needs to be delivered. For cervical cancer, a clear consensus exists regarding what anatomical areas should be included within this CTV; tumour, cervix, uterus, bilateral parametria and upper vagina for primary CTV and common iliac, internal and external iliac, upper presacral and obturator nodes for nodal CTV. However, variation in delineation of this CTV has been documented with up to 19 cm differences and two fold volume differences [9-11]. This can lead to significant differences in doses delivered to areas at risk of microscopic disease if IMRT is applied [12] but can be reduced by clear guideline use [13]. Variations in brachytherapy delineation have also been documented that can be large enough to alter treatment optimisation [14,15]. This delineation accuracy remains an important aspect of IMRT delivery and on-going efforts to minimise this should be adopted. Such methods to reduce this variation include protocol publication, quality assurance (RTQA) within trials, and national and international delineation training courses.

Variation in shape and position of pelvic organs is seen during a course of chemo-radiation, primarily due to bladder and rectal filling variations. Within the radiation therapy planning process, margins are applied to CTV to create a planning target volume (PTV) to account for daily set up variation and motion within the pelvis between and during treatments. Many studies have attempted to quantify pelvic organ motion showing up 4 cm movement in some directions [16,17]. Margins of this size are not clinically applicable as overlap with OARs would increase greatly thereby increasing toxicity. Other compensation methods are therefore needed. This includes daily image guidance, adaptive planning and strict bladder and bowel preparation, all of which involve increased resources and clinical input. Even centres with years of experience in daily image guided adaptive radiation therapy still rely on backup 3-dimensional conformal plans for days where movement is larger than predicted [18].

Due to the fact that IMRT has only recently been introduced into routine practice there remain some uncertainties regarding the magnitude of potential late effects. These include the peripheral dose increase consequences and the effects of IMRT on late second cancer risk. Peripheral dose does increase by 0.12% of prescribed dose with IMRT [19], an effect which is less with lower energies. The clinical consequence of this is currently unclear. The absolute risk of second cancers is increased by 0.75% at 10 years with IMRT, again a figure which is higher if higher energy is used [20]. Structured follow up and data collection in the years to come will be vital to monitor the true late consequences of IMRT.

Brachytherapy is an integral part of cervical cancer chemo-radiation. Traditionally, dose was applied in a standard distribution prescribed to an anatomical point (point A). In the last 10 years IGBT has been introduced where dose is prescribed to a target volume (high risk CTV) and the use of magnetic resonance imaging (MRI) and interstitial needles facilitates more tailored dose delivery [21]. The retro-embrace data has shown a potential increase in overall survival of approximately 10% as well as increase in pelvic control [22]. This is exciting but does open the question of how high a dose do we need to deliver and how much pelvic control contributes to survival. The on-going EMBRACE2 study may help to answer these questions. When reviewing the use of IGBT the variation of resources available across the world is highlighted. Even within developed countries variation is

significant [23] and must be addressed through collaboration and setting of agreed standards.

Other methods of improving chemo-radiation outcomes for locally advanced cervical cancer may be the addition of chemotherapy before or after radiation. This is being investigated in the international randomised controlled trials INTERLACE and OUTBACK respectively. The potential impact of alternative radiosensitisers is another area of current interest with early phase studies underway.

Within the field of radiation therapy for locally advanced cervical cancer we continue to strive to improve outcomes. There are therefore many exciting technological and pharmacological advances which could increase cure rates and decrease toxicity. However, to ensure the best outcomes, these new techniques and treatments should be introduced with a measured systematic approach and a full appreciation of their limitations ideally within international collaborative studies.

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