Two landmark studies report on success of using image-guided brachytherapy to treat cervical cancer

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Geneva, Switzerland: Two large, landmark radiotherapy studies have shown that it is possible to treat cervical cancer effectively with high doses specifically adapted to each tumour, and with fewer serious side-effects to the surrounding normal organs.

In two presentations today (Saturday) and tomorrow (Sunday) researchers will tell the 2nd Forum of the European Society for Radiotherapy and Oncology (ESTRO) that image-guided brachytherapy is able to deliver very high doses, which prevent the tumour from growing in over 90% of patients, with few serious side-effects.

One of the problems with radiotherapy for cervical cancer is that the vagina receives a high dose of radiotherapy, which can cause symptoms such as vaginal dryness, vaginal narrowing and shortening, with a loss of flexibility (stenosis), vaginal inflammation (mucositis), bleeding, or a hole in the wall of the vagina (vaginal fistula) – one of the most serious but rare complications. The bowel and bladder can also be affected by radiotherapy for cervical cancer.

Image-guided brachytherapy involves delivering radiotherapy to the tumour by placing a radioactive source in an applicator, positioned internally in the tumour region. Imaging, either by repeated computer tomography (CT) scans or preferably magnetic resonance imaging (MRI), is used at the time of brachytherapy in order to delineate both the

tumour and organs at risk in relation the applicator. This enables radiation oncologists to measure and evaluate the tumour response to the treatment, and adjust the dose accordingly, while sparing surrounding organs.

However, until now, there have been few studies investigating the relationship between the dose of radiotherapy and the effects it has on the vagina during brachytherapy for cervical cancer, according to Ms Kathrin Kirchheiner (MSc), who will be reporting on the international, multi-centre prospective clinical trial EMBRACE (European and international study on MRI-guided brachytherapy in locally advanced cervical cancer) at the meeting today (Saturday).

"To date, the EMBRACE study has followed 523 patients in 19 centres for an average of 14 months to establish a benchmark for clinical outcome with regard to control of the tumour's growth, patient survival, adverse effects of treatment and quality of life," said Ms Kirchheiner, who is a PhD student in the Department of Radiotherapy at the Medical University Vienna (Austria).

Patients with cervical cancer that had started to spread from the original site to nearby tissues and lymph nodes (locally advanced cancer) underwent external beam radiotherapy, chemotherapy and MRI-guided brachytherapy. The vagina and the effects of the treatment on it (morbidity) were assessed at the start of treatment, every three months afterwards for the first year, once every six months in the second and third year, and annually thereafter. MRI was used to assess the amount of dose being delivered to the upper part of the vaginal wall.

"Our results show that severe vaginal side-effects are rare," said Ms Kirchheiner. "The majority of patients are likely to experience mild to moderate (grade 1 or 2) vaginal morbidity in the first two years after the end of treatment. The most frequently reported symptom is vaginal

shortening and narrowing in the upper vagina. We performed a dose response analysis to measure the relationship between the amount of dose delivered to the upper vaginal wall and the probability of vaginal morbidity and found that with increasing dose to this region, the probability for moderate vaginal morbidity increases significantly."

This is the first time that the occurrence of mild and moderate side-effects on the vagina have been systematically recorded and related to the amount of radiation dose in this way. "This is important for patients because studies on their quality of life have shown that mild and moderate vaginal symptoms and associated sexual dysfunction can cause long-term distress in cervical cancer survivors, but until now a clear dose response relationship had not been established.

"Brachytherapy is an essential part of the curative treatment of locally advanced cervical cancer, because of the high dose that can be delivered to the tumour while sparing organs at risk of damage from the treatment. With the possibility of dose adaptation and optimisation in image guided adaptive brachytherapy, a highly individualised and tailored treatment has become possible, comparable to the targeted, personalised therapies in medical oncology," concluded Ms Kirchheiner.

The second study is retro-EMBRACE, which collected data on 592 patients in 12 institutions in Europe and Asia. Associate Professor Kari Tanderup, of the Department of Oncology at Aarhus University Hospital, Denmark, will be reporting results from this retrospective study tomorrow (Sunday).

"When using radiotherapy to treat cervical cancer there is a certain distribution of absorbed dose within the body and it is essential to know the dose level needed for local control of the tumour. However, there has been a wide range of brachytherapy schedules throughout the world with application of different dose levels for cervical cancer, and there has

been limited evidence for a clearly defined dose response relationship," she will say.

"One of the reasons is that most cervical cancer brachytherapy experience has been based on planning on radiographs and not 3D imaging. With radiographs it is difficult to assess the dose to the tumour precisely, whereas with MRI or CT guided brachytherapy is it now possible to assess the dose to the tumour with much higher precision. With the retroEMBRACE study it has been possible for the first time to assess a dose response relationship in a large number of patients in a multicentre setting. We looked at different dose levels and found a significant increase in local control with higher doses."

Cervical cancer patients were treated with external beam radiotherapy, chemotherapy and image-guided adaptive brachytherapy (IGABT) based on MRI or CT scans. The amount of residual tumour (known as "high risk clinical tumour volume" or HR CTV) was assessed after the external beam radiotherapy in order to plan IGABT, and to target the residual tumour. "By taking the residual tumour into account we are able to tailor the brachytherapy dose to the individual patient and to the individual tumour response. We call this 'adaptive radiotherapy' because we adapt our treatment to changes which occur during radiochemotherapy," explains Prof Tanderup.

"Our study shows very clearly that the higher the dose the better the tumour's response to the brachytherapy for the entire patient population. It is possible to obtain local control in over 90 percent of patients with application of very high doses of over 90Gy. Brachytherapy is a very appropriate technique to obtain highly focused boost doses, and retroEMBRACE shows that it is actually possible to deliver doses greater than 90Gy for a significant fraction of the patients. It would not be possible to achieve doses greater than 90Gy with external beam radiotherapy without significantly increasing dose to critical organs, and

therefore brachytherapy is a crucial component of radiotherapy in cervix cancer. Furthermore, the study also enables us to analyse results in patients with different risks of their tumours recurring or continuing to grow."

She will conclude: "The retroEMBRACE study is important for the community because it establishes evidence for a dose response relationship in locally advanced cervical cancer; it shows that local control in over 90 percent of patients can be obtained with the use of MRI-guided brachytherapy; retroEMBRACE makes it possible for institutions to change their dose prescription in order to optimise the balance between local control and adverse side-effects; and it demonstrates that the adaptive target concept which has been developed for MRI-guided brachytherapy is robust in a multicentre setting."

President of ESTRO, Professor Vincenzo Valentini, a radiation oncologist at the Policlinico Universitario A. Gemelli, Rome, Italy, commented: "This is a tangible example of how large series of data, collected by collaborative networks, and high quality treatment that takes advantage of the latest advances in imaging, can help radiation oncologists to adapt treatments to individual patients so as to give them the best chance of a cure with fewer side-effects."

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