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Opinion

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The Use of Localised Vaginal Drug Delivery as Part of a Neoadjuvant Chemotherapy Strategy in the Treatment of Cervical Cancer

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Cervical cancer is the third most prevalent cancer in women globally, with 529,000 diagnosis and 275,000 deaths each year. It is especially prevalent in developing countries where approximately 85% of cases arise due to the lack of cervical cancer prevention and control programs. In developed countries, where women have access to resources capable of detecting and treating precancerous lesions, the number of cases is reduced by approximately 80%.[1] Cervical cancer can be characterised, depending on how far it has spread, from stage 0 (precancerous), also called Cervical Intraepithelial Neoplasia (CIN), where abnormal cells are found in the innermost lining of the cervix and have the potential to become cancerous, through to stage 4, where the cancer has spread to the bladder, rectum or other parts of the body, such as the lungs. In developed countries, there are currently two methods used to prevent cervical cancer from developing to an advanced stage: (1) the distribution of HPV vaccines that are mainly directed against HPV types 16 and 18[2] and (2) screening methods, such as Papanicolaou test (Pap smear), which involves the collection of exfoliated cells from the cervix, which are then examined for cellular abnormalities. This enables identification of CIN before they begin to develop into cervical cancer.[3]

Strategies for cervical cancer treatment will depend on the women's general health as well as the type, stage and grade of the cancer and usually involve a combination of surgery, chemotherapy and radiotherapy.[4,5] Increasing numbers of women of reproductive age are being diagnosed with cervical cancer, with approximately 15% of all cervical cancers and 45% of stage IB cancers treated using surgery occurring in women under the age of 40[6] The two main surgical procedures in fertility sparing treatment are Vaginal Radical Trachelectomy (VRT) and Abdominal Radical Trachelectomy (ART). A review of fertility sparing surgery by Rob et al. demonstrated that radical trachelectomy is safe with similar risk of recurrence to that of radical hysterectomy in selected cases of small volume tumours measuring less than 2 cm in diameter.[7] Fertility sparing treatment is only offered to those women that meet a certain criteria such as a diagnosis of early stage cervical cancer where the tumour is limited to the cervix with no evidence of pelvic lymph node metastasis and/or other distant metastasis and a tumour size of less than 2 cm.[8] Adherence to these criteria is important in reducing the risk of recurrence, which is significantly higher in tumours greater than 2 cm.[9-11] The recurrence rate in women with tumours greater than 2 cm is 20.8% after VRT and 20% after ART compared to 2.9% and 1.9% respectively in tumours less than 2 cm.[7]

Systemic administration of Neoadjuvant chemotherapy (NAC) can be used to downstage the tumour before fertility sparing surgery, thus decreasing the tumour volume and allowing for a much smaller tumour to be removed. A review of three clinical trials investigating NAC and fertility sparring surgery involving 33 women (24 with tumours greater than 2 cm) demonstrated that 26 of the women had their fertility spared, which resulted in 18 conceptions and 16 deliveries, 4 of which were premature, while only 1 of the women had a recurrence of the cancer.[7] The response rate of advanced cervical cancers to NAC has been shown to be

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between 60 and 95%[12-14] and a recent Cochrane review on NAC plus surgery (radical hysterectomy and radical trachelectomy) versus surgery alone demonstrated that both the overall survival and progression-free survival where significantly improved, while local recurrence was reduced with the use of NAC.[15] However, parenteral administration of chemotherapeutic drugs has an adverse effect on patients due to systemic side effects. Localised delivery of chemotherapeutic drugs offers a number of advantages over parenteral administration such as direct delivery to the site of action resulting in a lower dose being required as well as a reduction in systemic side effects and increased drug stability as it remains in the delivery device until released.[16] The location of the cervix makes it easily accessible through the vagina and allows for the non-invasive implantation of a localised drug delivery device adjacent to the cancerous tissue either before resection, to reduce tumour size, or after resection to reduce the risk of recurrence.

The vagina has been used to deliver drugs for a range of clinical and research applications, including contraception, vaginal infections and HIV prevention, with many different vaginal formulations such as gels, creams, pessaries, suppositories, rings, films and tablets available.[17-23] Furthermore, a number of these delivery systems have already been investigated for the localised delivery of chemotherapeutic drugs to the cervix.[24-30] The range of formulations available offers flexibility in the type of drug that can be delivered and its dosing regimen as well as allowing the treatment and dosing to be tailored to the needs of the patient.

Although fertility-sparring surgery may see the greatest benefit from localised drug delivery as part of a NAC treatment strategy it could also be used as part of a standard treatment protocol for locally advanced bulky cervical tumours to reduce tumour size before surgery (radical hysterectomy) allowing for increased cancer free margins, reduced morbidity and the avoidance of radiotherapy, as well as post-surgery (radical trachelectomy or radical hysterectomy) to reduce recurrence by eliminating any cancerous tissue left behind.

Cervical cancer is an excellent candidate for localised drug delivery as due to regular screening most cases are diagnosed when the cancer is confined to the cervix. Furthermore, due to its location it easily accessible through the vagina allowing for the administration of any vaginal drug delivery device or formulation. The therapeutic use of these drug delivery devices and formulations would vary depending on the patient's needs and could form part of an NAC treatment regimen for those patients requesting fertility sparing treatment or undergoing a standard treatment protocol. Any vaginal drug delivery device or formulations could be used to provide local delivery of a chemotherapeutic drug to the cervix and each has its own advantages and disadvantages from improved patient compliance to being expensive to manufacture. Furthermore, localised delivery of chemotherapeutic drugs directly to the cervix will improve the patients overall quality of life both during and after treatment allowing for the patient to recover much quicker resulting in reduced hospital presentations and admissions, which could have a cost saving effect on the global healthcare system. With an increase in the number of NAC clinical studies being performed, albeit using systemic delivery of chemotherapeutic drugs, the benefits of NAC in conjunction with fertility sparring surgery and standard surgery are being recognised. Therefore, within the next five to ten years NAC in conjunction with either fertility sparing surgery or a standard treatment regimen will be the main cervical cancer treatment protocol, especially for those women who have a tumour size greater than 2 cm, to both preserve fertility and reduce recurrence. This will lead to the realisation that when it comes to the treatment of cervical cancer localised drug delivery is much more beneficial than systemic drug delivery, due to an improved quality of life for the patient during treatment, faster recovery times, reduced recurrence and better patient compliance. Therefore, over the next 5 to 10 years there will be a rise in the number of NAC clinical trials which compare localised delivery to systemic delivery in reducing tumour size, which will lead to an increase in the development, testing and regulatory approval of vaginal dosage forms for the localised delivery of chemotherapeutic drugs to the cervix.

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