Synchronous oligometastases in cervical cancer: a case report

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Incidence and mortality of cervical cancer in South Africa is still very high and 4-6% of women present with FIGO stage IVB disease. However, the management of oligometastatic cervical cancer is not well decribed in literature. Treatment of stage IVB cervical cancer is individualised, but it mainly involves palliative systemic chemotherapy with a median survival time of about ten months. There is a growing body of evidence showing that in women with low volume oligometastatic disease, curative doses of radiation therapy to the pelvis and metastatic sites with or without chemotherapy can prolong survival significantly. Since South Africa is one of the few countries in Africa with functional chemoradiation therapy facilities, there is a need to review this evidence and see if the standard of care has to be changed in women with oligometastatic cervical cancer.

Keywords: cervical cancer, synchronous, metachronous, oligometastases, radical chemoradiation

Introduction

The incidence and mortality of cervical cancer in South Africa is still very high. In 1998–1999, there were 6 061 and 5 203 new cases of cervical cancer respectively giving an age-standardised incidence rate (ASIR) of 42 and 35/100 000 respectively. Mortality in the two-year period was nearly 60%.[1] Worldwide, 85% of cervical cancer deaths occur in resource-limited countries.[2] In these countries, cervical cancer is usually diagnosed late, and a shortage of chemoradiotherapy facilities to treat women with advanced disease compounds the problem.[3] If there are no contraindications, the treatment of choice in early-stage cervical cancer is surgical although radiotherapy has been shown to be equally effective.[4] In women with locally advanced disease, chemoradiation treatment is the standard of care.[5,6] In South Africa, 4–6% of women present with stage IVB disease.[7,8] However, oligometastasis to the musculoskeletal site is rare. Treatment of stage IVB cervical cancer is individualised, but it mainly involves palliative systemic chemotherapy with a median survival time of about 10 months.[9] However, there is a growing body of evidence showing that in women with low-volume oligometastatic disease curative doses of radiation therapy to the pelvis and metastatic sites with or without chemotherapy can prolong survival significantly. Since South Africa is one of the few countries in Africa with functional chemoradiation therapy facilities, there is a need to review this evidence and see if the standard of care has to be changed in women with oligometastatic cervical cancer. We report on a case of a 34-year-old woman with cervical cancer and synchronous oligometastases to the musculoskeletal system. We discuss her outcome and also review the literature on the evolving treatment of oligometastatic gynaecological malignancies.

Case report

### Initial presentation

A 34-year-old woman, G3P3, presented to a secondary-level hospital with abnormal vaginal bleeding for two months. She had been on Depo-Provera contraception for 10 years. She defaulted on her last dose as she suspected that it was the cause of her abnormal bleeding. She had had no prior cervical screening but a Pap smear taken when she started bleeding showed high-grade squamous intraepithelial lesion (HSIL). She had no chronic medical problems and her only surgical history was excision of a right upper arm lipoma. She had no smoking history. On gynaecological examination, a fungating exophytic tumour replacing the cervix was seen and a punch biopsy was taken. Her haemoglobin count was 5.2 grams per decilitre (g/dl); she was transfused five units of packed red blood cells and referred to our unit. On arrival, she had an elevated diastolic blood pressure of 133/106, tachycardia of 135 beats per minute and a temperature of 36.6 °C. Her chest was clear and on cardiovascular examination she had no gallop rhythm or murmurs. Her abdomen was soft and non-tender. On vaginal and rectal examination, she had a 6 × 8 cm exophytic fungating tumour replacing the cervix, which was confined to the upper two-thirds of the vagina with bilateral pelvic sidewall involvement. She had normocytic hypochromic anaemia of 7.7 g/dl with normal renal and liver function tests. Her syphilis and HIV screening tests were negative. Chest X-ray and cystoscopy did not show any metastases or bladder invasion respectively. Abdominal imaging via ultrasound scan showed a normal liver and she had no hydroureteronephrosis. The punch biopsy results showed moderately differentiated cervical squamous cell carcinoma. She was clinically staged as FIGO stage IIIB. She consented to treatment with pelvic radiotherapy, which was the recommendation of our tumour board. Prior to starting her treatment, she had been admitted twice with severe anaemia and transfused a total of six units of packed red blood cells (excluding the five units she received from the referral hospital). She completed her treatment on November 14, 2016. The plan was for routine follow-up in our combined radiation and gynaecology oncology clinic.

Synchronous right upper arm oligometastases

Two months after completion of her radiation treatment, the patient presented with a shoulder abscess on the right arm,
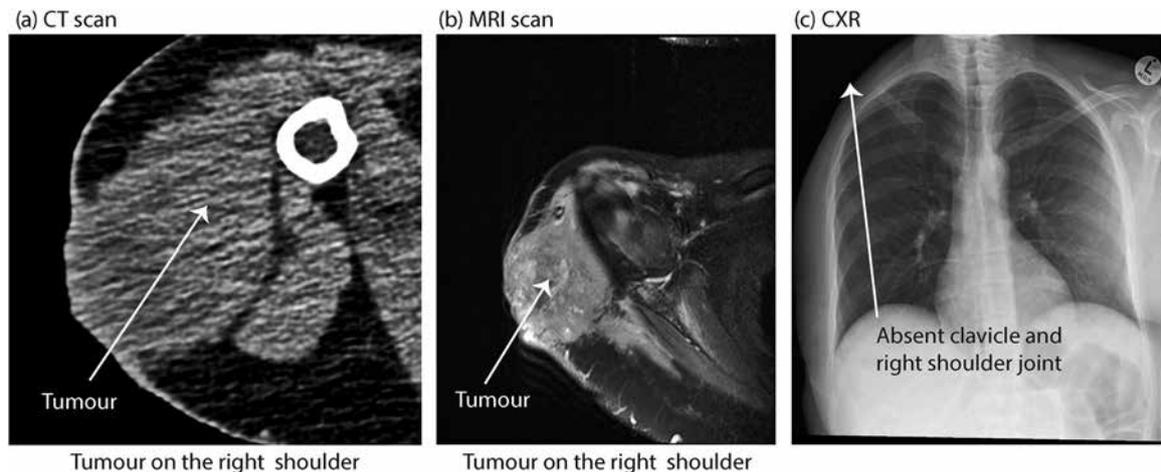
Figure 1: Imaging of the right shoulder before and after surgery.

for which she had incision and drainage. *Enterobacter cloacae* complex, sensitive to ciprofloxacin, was isolated from the wound and she received appropriate treatment. However, three months after the incision and drainage the wound had not healed and this prompted a biopsy. The results confirmed metastatic squamous cell carcinoma of cervical origin. Clinical examination and computed tomography (CT) scan of the pelvis, abdomen and chest excluded local persistent disease and other regional or distant metastatic sites (see figure 1). A magnetic resonance imaging (MRI) scan of her right shoulder confirmed a large deltoid mass with reactive changes in the proximal humerus and erosion of the acromion (see figure 1). Her bone scan did not show any suspicious areas.

Tumour board discussion
Her case was re-discussed by our tumour board. A decision was made to treat her with platinum-based chemotherapy with or without radiation treatment to the metastatic site. However, after her second cycle of chemotherapy she developed wound sepsis and the chemotherapy was stopped. She experienced intractable bleeding from the wound, and she received four fractions of palliative radiation therapy totalling 28 Gray (Gy) to the metastatic site. Although the bleeding was controlled with radiation therapy, the wound remained septic.

She was referred to plastic surgeons for an opinion on possible excision. Their opinion was that, due to its size and location, the lesion was not amenable to local excision. Since she had oligometastatic disease (based on whole-body CT scan and bone scan), she was offered a salvage right upper limb forequarter amputation. Positron emission tomography (PET) combined with CT scan was considered, but the tumour board was of the opinion that since the surgery was indicated for sepsis further imaging was not going to change her management. The patient and her family were agreeable to the plan. Her histology report and slides were reviewed by the tumour board (see figure 2). The gross specimen showed an arm amputation with a 122 mm × 80 mm × 60 mm tumour in the deltoid area involving the anterolateral aspect of the upper arm. There was overlying skin ulceration. Yellow-green pus was present within the tumour. The tumour was clear of all resection margins. The neurovascular bundles, the humerus and the shoulder joint were also uninvolved. The microscopic examination showed ulcerated skin with an underlying deposit of moderately differentiated non-keratinizing squamous cell carcinoma involving the dermis of the skin, the underlying subcutaneous adipose

tissue and skeletal muscle. The tumour focally extended to the epidermis. The tumour was composed of nests and large islands of non-keratinising squamous cells with large areas of central necrosis. There was no sarcomatous differentiation, and there was no involvement of the neurovascular bundles. The margins were clear of the tumour (superior 4 mm, inferior margin > 25 mm, lateral 33 mm and medial >22 mm). The tumour showed positive immunostaining for p63 and p16, consistent with squamous differentiation and cervical origin. She missed her scheduled postoperative appointment but came to the combined radiation and gynaecological oncology clinic three months after her surgery, and she had fully recovered. She was seeing an occupational therapist for rehabilitation.

Progress after the forequarter amputation
Five months after her surgery she presented again to the combined radiation and gynaecological oncology clinic with generalised body pain and lumps on her body. Her Eastern Cooperative Oncology Group (ECOG) performance status was 3–4. On clinical examination, she had a 12 × 12 cm hard metastatic nodule in her right axilla, an 8 × 6 cm right flank superficial metastatic mass and an 8 × 6 cm metastatic nodule on the inner aspect of her right thigh. Due to her poor performance status, she was deemed unfit for palliative chemotherapy, and she was offered best supportive care. As a result of the amputation of her dominant upper limb, she required assistance with activities of daily living (ADLs) all the time, which compromised her privacy and quality of life. A social worker arranged her registration with a local hospice and home-based care services. The patient died from the disease 10 months after diagnosis of synchronous metastatic disease.

Discussion
Oligometastases refers to a condition in which the patient shows distant relapse in only a limited number of regions. Distant metastatic disease can either be synchronous or metachronous. Synchronous disease is defined as distant metastases occurring within, and metachronous disease beyond six months of the primary diagnosis.

The standard of care for women with metastatic cervical cancer is systemic platinum-based combination chemotherapy, but response rates are low and median survival time is < 1 year.[9] With the addition of bevacizumab, a humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody to standard chemotherapy, median overall survival time is still less
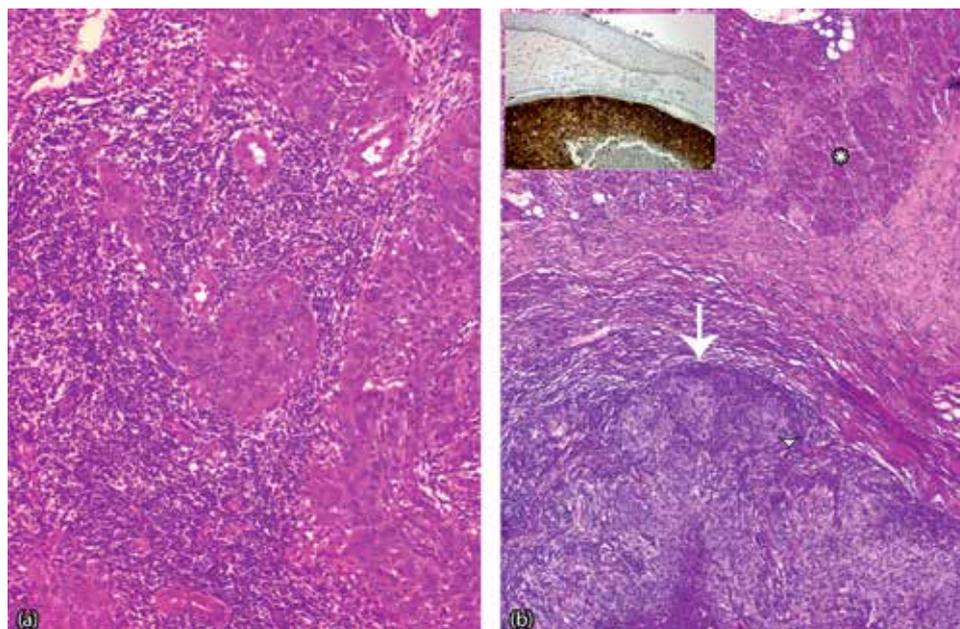
Figure 2: Cervical biopsy and deltoid muscle metastases histology microphotographs.

than 18 months.[10] In these two studies, chemotherapy was given until there was disease progression or severe toxicity and for a shorter duration in those who did not respond.[9,10] There is a growing body of evidence of the use of definitive radiation therapy in oligometastatic disease in melanoma, non-small cell lung and breast cancer resulting in good local control and prolonged survival.[11–13]

There is recently published literature exploring the use of definitive radiation therapy with or without chemotherapy in women with oligometastatic gynaecological malignancies. In a single institution study, the outcome of 38 women who had either synchronous or metachronous metastatic cervical cancer involving ≤ two extra-pelvic or para-aortic sites is described. The metastatic sites included lung, supraclavicular and mediastinal lymph nodes. To be eligible, they needed to have received definitive treatment of their primary cervical cancer with concurrent chemoradiation (which included extended para-aortic fields in the majority of cases) and brachytherapy. On top of that, the women were included only if they had received treatment with definitive intent of oligometastatic sites, defined as a radiotherapy dose ≥ 50.4 Gy (median 60 Gy). The median overall survival (OS) was 50.7 months from the end of radiation therapy, with 2-year and 3-year OS rates of 74% and 65% respectively.[14] Regional or distal (or both) disease progression occurred in half of the patients at a median time of two years after definitive radiotherapy treatment.[14]

Another study compared outcomes in two groups of women with metastatic cervical cancer. One group had para-aortic as well as left supraclavicular lymph node involvement. The other group had para-aortic lymph node involvement only. The group with left supraclavicular lymph node involvement was treated with a mean radiotherapy dose of 59.4 Gy to the para-aortic and left supraclavicular areas and 50.4 Gy to the pelvis, followed by 30 Gy of high-dose-rate brachytherapy in 6 fractions. The group without left supraclavicular lymph node involvement received the same dose to the para-aortic area and pelvis followed by intracavitary brachytherapy. Platinum-based chemotherapy was simultaneously given to all patients. In the group of women with oligometastatic supraclavicular lymph node disease, radical chemoradiation to the pelvis and metastatic sites was associated with a median OS of 32 months and 3-year OS rate of 49%.[15]

As stated before, the standard of care in patients with stage IVB cervical cancer is systemic chemotherapy. However, one case series looked at the use of chemotherapy and radical radiation therapy to the pelvis in 24 women with synchronous metastatic cervical cancer with metastases to lung, liver, bone or groin lymph nodes. All the patients received a radical dose of pelvic external beam radiotherapy with or without brachytherapy. The mean dose to point A was 73.9 ± 19.2 Gy (mean ± standard deviation) They showed a three-year OS rate of 44% and five-year OS rate of 22%.[16] Use of stereotactic body radiation therapy (SBRT) in 85 women with recurrent or oligometastatic cervical cancer demonstrated a median OS of 32.7 months and two-year OS of 57.5%.[17]

In the studies described above, PET/CT scan was not mandatory to diagnose oligometastatic disease.[14–16] The improvement in overall survival was achieved in these patients without metastasectomy of oligometastatic disease.[14–16] However, the Royal College of Radiologists recommends PET/CT scan in patients with oligometastatic colorectal disease, sarcoma and melanoma who are planned for metastasectomy.[18]

Careful patient selection, excellent local control, low-volume disease at oligometastatic sites and advances in radiation therapy have been postulated as the reasons for the improved outcome in these patients.

In our patient, the outcome was not as good as described in the studies mentioned earlier. We attributed this to the fact that she was not able to finish her chemotherapy due to local sepsis on the metastatic site and radiation therapy was given in an emergency setting to control bleeding, and she received palliative doses only. She also had high-volume metastatic disease. However, we decided to report on her case to highlight the evolving data on the optimal management of these women.

Conclusion

There is some accumulating evidence that definitive radiation therapy with or without chemotherapy is associated with excellent local control and prolonged survival in carefully selected patients with oligo metastatic cervical cancer. Surgery alone has no clear role, and it should be avoided.

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