Case Report: Management of isolated Para-aortic lymph nodal recurrence after primary chemo-radiotherapy treatment for vaginal clear cell carcinoma

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Abstract
Abstract: We report a case of eradication of isolated para-aortic lymph nodal (PALN) recurrence, after 22 months, in the aortic region below the left renal vein (LRV) in a 66-year-old patient diagnosed with stage 3B clear cell carcinoma in the vagina in 2019 and treated with primary chemo-radiotherapy. During the routine follow-up scans, an enlarged left Para-aortic lymph node was detected which was showed to be an active disease on PET/CT scan with no evidence of local recurrence in the pelvis. After MDT discussion and discussion of the management options with the patient, she opted for surgery. Midline laparotomy and infra-renal Para-aortic lymphadenectomy were done. Estimated Blood Loss (EBL) was 500 ml. The operative time during the surgical procedure was 245 minutes. No intraoperative complications and the recovery period was unremarkable. The patient was discharged 6 days postoperatively. The Histology revealed that 2/7 lymph nodes are positive. The postoperative MDT outcome was to consider adjuvant PA lymph node radiotherapy as 2/7 nodes positive and cannot be certain of R0 resection given lymph channels. In June 2023, the patient completed adjuvant radiotherapy to the paraaortic strip 45Gy in 25 fractions with a boost to a nodal bed. Postoperative CT chest, abdomen pelvis will be arranged as baseline to monitor the progress.

Categories: Oncology
Keywords: recurrence, vaginal cancer, lymph nodes, lymphadenectomy, para-aortic

Introduction
Primary vaginal cancer is very rare and accounts for about 1-2% of all women gynaecological cancers [1]. Primary vaginal cancer is strictly defined as a disease without evidence of vulval or cervical cancer or a history of either within the past 5 years. 80-90% vaginal lesions originate from cervical or vulvar lesions or other local sites such as the endometrium, ovary, bladder, or rectosigmoid. Distant sites of metastasis include the breast, colon, and pancreas. When primary vaginal cancer is suspected, a biopsy should be done for histopathology confirmation [1-3].

The pathways of carcinogenesis of vaginal cancer can be divided into human papillomavirus (HPV) induced and non-HPV induced [4]. The HPV 16 virus strain accounts for most HPV-positive patients [5]. Within the HPV DNA, the activity of the viral reading frames E6 and E7 create proteins that interfere with critical points of the cell cycle points. E6 interferes with suppressive tumor protein p53 and E7 interferes with retinoblastoma protein (pRB). These are significant factors in HPV-related neoplasia, including primary vaginal cancer. The E5 protein may also play a role in the immune evasion [6].

Historically, diethylstilbestrol (DES), a synthetic estrogen used to prevent preterm births and miscarriages, has been associated with clear cell adenocarcinoma of the vagina in offspring [7]. The incidence of this cancer has declined since the discontinuation of the routine use of DES in the 1970s.

Case Presentation
The background history of our case: A 66-year-old postmenopausal patient, with a history of vaginal bleeding. The patient had hysterectomy and oophorectomy in 2006 for perimenopausal bleeding and the histology showed adenomyosis and endometriosis. The patient had a history of left breast carcinoma, multifocal, 1mm, grade 2, ER-positive HER negative, and had in 2014 wide local excision and positive axillary nodes (re-excision and clearance) followed chemo-radiotherapy. Adjuvant therapy, (Arantrazole), was given for 5 years. In 2019, the patient developed a pulmonary embolism, initially, she was on Clexane which shifted to Rivaroxaban. She Had a vaginal biopsy in 2014 and the histology showed vaginal adenosis. In 2019, the patient was under the care of the urology team for investigation of Haematuria, whilst in theatre, a vaginal vault mass has been seen on Examination under anaesthesia, a biopsy was taken and the histology showed clear cell carcinoma (presumably arising in endometriosis) of the top of the vagina. The tumour cells are positive for CK7 and PAX8. They are focally positive for ER, P16, and P53. Negative markers are GATA3, PR, CK20, and CDX2. CT of her abdomen and pelvis showed a vaginal vault lesion and left-sided lymph node enlargement making this stage 3b at least. The decision made after MDT was for primary chemoradiotherapy.

Treatment summary:
- External beam radiotherapy to the pelvis, 45Gy in 25 fractions, completed in May 2019 followed by interval chemotherapy with Carboplatin and Paclitaxel between June and September 2019
- High Dose Rate (HDR) brachytherapy and examination under anaesthesia, in October 2019, receiving 14Gy in 2 fractions.

Good response to treatment with reduction in the size of the pelvic tumour and the lymph node. In 2020, no obvious disease was detected in her follow-up scans.

In August 2021, a follow-up MRI pelvis showed non-significant enlargement of the left Para-aortic lymph node (PALN) detected (6mm) with no evidence of local recurrence in the pelvis. The size of the PALN remained stable in February 2022 imaging but 6 months later, an MRI pelvis in August 2022 showed left para-aortic lymphadenopathy, slightly increased in size (8 mm) in comparison with the August 2021 scan with still no evidence of local recurrence in the pelvis. The case has been discussed in MDT and the decision made to arrange a PET scan.

Nuclear Medicine Whole body PET FDG CT scan:
The scan was done in September 2022 and showed left para-aortic lymphadenopathy consistent with active disease. No other site of concern (figure 1).

MDT discussion

The management options were discussed in the MDT meeting. The options discussed are either to go for radiotherapy avoiding the surgical risks but surgery in the future for recurrence could be very difficult and associated with many more risks. The second option is to have surgical removal of lymph node, followed by
either interval observation or straight to radiotherapy +/- chemotherapy. The recommendation from MDT was the surgical option. After a discussion of each option, pros and cons, the patient opted for the surgical option.

Surgery

In November 2022, the patient had EUA, Midline laparotomy. Para-aortic lymph nodes were found densely adherent to the aorto-caval ligament/bone. Complete infra-renal Para-aortic lymphadenectomy was done. The operative time during the surgical procedure was 245 minutes and EBL was 500 ml. No intraoperative complications and the recovery period was unremarkable. The patient was discharged on day 6 postoperative. The Histology result revealed that 2/7 lymph nodes are positive (figure 2).

Postoperative MDT outcome

The MDT meeting decision was to consider adjuvant PA lymph node radiotherapy as 2/7 lymph nodes are positive and we cannot be certain of R0 resection given lymph channels. In June 2023, the patient completed adjuvant radiotherapy to the Para-aortic strip 45Gy in 25 fractions with a boost to a nodal bed. Postoperative CT chest, abdomen pelvis will be arranged as baseline to monitor the progress moving forward.

Discussion

Pelvic and aortic lymphadenectomy is performed during surgical treatment of gynaecological cancers for their prognostic and therapeutic significance [8]. These procedures are performed close to multiple vascular structures with a high risk of intraoperative injuries and bleeding. Vascular injuries are the most potentially catastrophic complications, frequently involving iliac veins [9,10] due to their anatomical variability complicated distributions, and their positions posterior to the common iliac artery bifurcation. Many retrospective studies showed the advantages of surgery in patients with a long disease-free interval, resectable disease (based on imaging), a limited number of metastatic sites, absence of ascites, and a good performance status [11]. However, the frequency of isolated lymph node recurrence (ILNR) is actually rare, between 1% and 6%. In these patients, surgery could be of particular benefit [12]. Blanchard et al. reported their experience with 27 patients with an isolated lymph nodal recurrence among 640 patients. They observed that after initial surgical treatment, the median progression-free survival (PFS) was 26 months. There was no difference in the 2-year survival rate after ILNR between the groups with early relapse and late relapse (before 24 months and after 24 months respectively). The time to relapse might not have its usual prognostic value and might not have the same value as in other sites of relapse.

Conclusions

Our experience suggests that surgery can be considered a safe and effective option for the management of isolated Para-aortic lymph nodal recurrence of vaginal cancer, with significantly low morbidity and short postoperative stay in the hospital, although it should be reserved for oncologic surgeons trained in extensive major surgical procedures; furthermore, large multi-center randomized clinical trials with long term follow-ups are still needed to confirm the overall oncologic outcomes of this procedure.

Additional Information

Disclosures

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References

6. Haręza DA, Wilczyński JR, Paradowska E: Human Papillomaviruses as Infectious Agents in Gynecological