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Peritoneal and port-site metastasis after RARP

Peritoneal and port-site metastasis following robotic-assisted radical prostatectomy

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Introduction

Peritoneal metastasis in the absence of further distant metastatic disease is exceedingly rare in prostate cancer. The majority of cases of peritoneal metastases result from widely disseminated metastatic disease, rather than following curative surgical intervention for localized disease.[1] Large population studies report the incidence of metastasis to the abdominal cavity and peritoneum as less than 1%.[2] The impact of minimally invasive surgery on oncological outcomes in prostate cancer has been a topic for discussion since its introduction. To our knowledge, there are no dedicated studies looking at robotic-assisted radical prostatectomy (RARP) and its association with peritoneal and port-site metastases. In relation to laparoscopic prostate surgery, there is a reported incidence of port-site metastasis of 0.1%. [3]

Only eight previous cases reports were identified to demonstrate peritoneal and port-site metastases following RARP. [4–10] We present a further four cases of peritoneal and port-site metastases following RARP, adding significantly to the published literature in highlighting this unusual occurrence.

Methods

The records of four cases of peritoneal metastasis following RARP identified across four hospital networks and three surgeons between May 2011 and October 2018 were identified. Patients who had undergone RARP and then subsequently developed peritoneal metastasis without evidence of any further distant metastatic disease were included. Clinical data including presentation, diagnosis, management and outcomes for these patients were obtained. A literature search was conducted using Medline and PubMed databases.

Results

Case 1

A 62-year-old male underwent salvage RARP in June 2018 for Gleason 4+5 prostate adenocarcinoma. This was in response to biochemical prostate specific antigen (PSA) recurrence following primary treatment with external beam radiotherapy (EBRT) seven years earlier. Table 1 outlines initial biochemical and histological characteristics of this and all subsequent cases. In November 2018 he presented with an acute small bowel obstruction. Diagnostic laparoscopy demonstrated extensive peritoneal metastasis and omental caking, biopsy was taken confirming metastatic prostate adenocarcinoma. He underwent an open total omentectomy, ileal resection and end ileostomy and was commenced on androgen deprivation therapy (ADT). Post-operative PSA was initially undetectable however, it has since risen to 0.21 in September 2019 with a small volume of intra-abdominal disease avidity concerning for recurrence on prostate-specific membrane antigen positron emission tomography (PSMA-PET) (Fig. 1).

Case 2

A 71-year-old male underwent a robotic-assisted cystoprostatectomy in October 2018 for Gleason 3+4 small cell carcinoma of the prostate (Table 1). In January 2019 he developed a subacute large bowel obstruction secondary to a retroperitoneal pelvic mass. Laparotomy was performed revealing significant peritoneal deposits which were debulked and bowel diversion was completed with formation of a sigmoid colostomy. Postoperatively the patient regained a degree of function although due to rapid disease progression he died in February 2019.

Case 3

A 69-year-old male underwent a RARP for Gleason 4+5 prostate adenocarcinoma in May 2011 (Table 1). He received salvage radiotherapy in August 2013 due to a climbing PSA to 4.49 ng/mL. In January 2019, he was again found to have a slowly rising PSA of 0.54 ng/mL. PSMA PET/CT identified a localized avidity within the anterior abdominal wall (Fig. 2), confirmed by needle biopsy as adenocarcinoma. A laparoscopic-assisted lower abdominal wall resection was performed to remove the well-circumscribed mass consistent with metastatic prostate adenocarcinoma on formal histology. Post operatively PSA remains undetectable.

Case 4

A 67-year-old male underwent a RARP for Gleason 4+5=9 prostate adenocarcinoma with significant ductal component in November 2013 (Table 1). Post-operatively he underwent adjuvant radiotherapy due to histology demonstrating significant multifocal extra-prostatic extension (EPE) and a PSA which remained elevated at 0.8ng/mL. In June 2014 he presented with worsening abdominal discomfort and a PSA of 445 ng/mL. CT of the abdomen and pelvis revealed peritoneal and omental deposits along with suspected malignant ascites. He

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was treated with androgen deprivation therapy and docetaxel. He eventually died in 2017 due to disseminated disease progression.

Discussion

Since the implementation of minimally invasive oncologic surgery, the potential for peritoneal and port-site metastases has been an area of concern. Several theories have evolved regarding intraoperative techniques and their contribution to development of peritoneal and port-site metastases. Such theories include the 'seed and soil' hypothesis and the 'chimney effect' whereby turbulent airflow around the port-site whilst establishing pneumoperitoneum may result in implantation of tumour cells.[11] Additional intra-operative factors such as traumatic tissue removal, tumour morcellation and absence of bag retrieval have been described linking laparoscopic surgery to increased risk of local tumour recurrence.[4] Emerging concern of peritoneal desiccation and impaired immune response secondary to use of dry CO_2 for insufflation has been the basis of several in vitro and animal studies. Nduka et al[12] examined this phenomenon in rats and demonstrated an increased rate of peritoneal tumour spread with cold, dry CO_2 insufflation when compared with warmed, humidified CO_2. Few randomized control studies have sought to further investigate these theories to-date, however a definitive association has not yet been established.[13] Newer devices such as the AirSeal®, which aims to reduce lens fogging and decrease smoke accumulation, also introduces higher CO_2 flow. Theoretically this may also impact tumour seeding however further evaluation is required. Of note, regarding our presented cases, AirSeal® was employed in case 2 only.

Many of these theories may additionally relate directly to minimally invasive robotic-assisted surgery. Reduced tactile feedback in robotic surgery has been postulated as a limitation to this technique, with suboptimal tissue handling being suggested, although not yet proven to be, a risk factor for peritoneal metastasis.[4] Although precautionary measures to avoid spillage of malignant cells into the operative field are taken universally, careful handling of high-risk tumours is imperative.

The biological characteristics of the primary tumour is likely to contribute to risk of peritoneal spread. Nguyen et al. examined peritoneal recurrence patterns between open and robotic radical cystectomy for the treatment of muscle invasive bladder cancer and an increased frequency of peritoneal carcinomatosis was found in the robotic cystectomy group (21%) when compared to open cystectomy group (9%).[14] Over half of cases included in their study were of solitary peritoneal metastases. The authors attributed this finding to a reflection of tumour biology rather than surgical technique; all cases being associated with ≥T3 staging. Lonnerfors et al. examined port-site recurrence following robotic gynaecological oncology surgeries in 475 women and identified a rate of 1.9% (n=9).[15] This study failed to provide a comparison between robotic and open or laparoscopic techniques however, but ultimately also found an association with high-risk histology. With respect the presented case series, histological patterns of disease with worse prognosis including the presence of small cell and ductal prostate carcinoma is notable. The remaining two cases exhibited Gleason score of 9,

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further substantiating that peritoneal metastasis seem more predominant in patients with high-risk tumours.

In conclusion, we present a series of peritoneal and post-site metastases following RARP in the absence of more widely disseminated disease. Larger studies are needed to evaluate any association between robotic-assisted surgery and peritoneal metastases. It is essential to explore any potential influences on tumour spread, including the iatrogenic impact from current surgical technique. Tumour characteristics should be considered a likely contributing factor. Modern imaging techniques such as PSMA-PET may enable better diagnosis and guide treatment.

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Figures and Tables

Fig. 1. Prostate-specific membrane antigen positron emission tomography for Case 1 demonstrating pathological uptake in left lower abdomen.
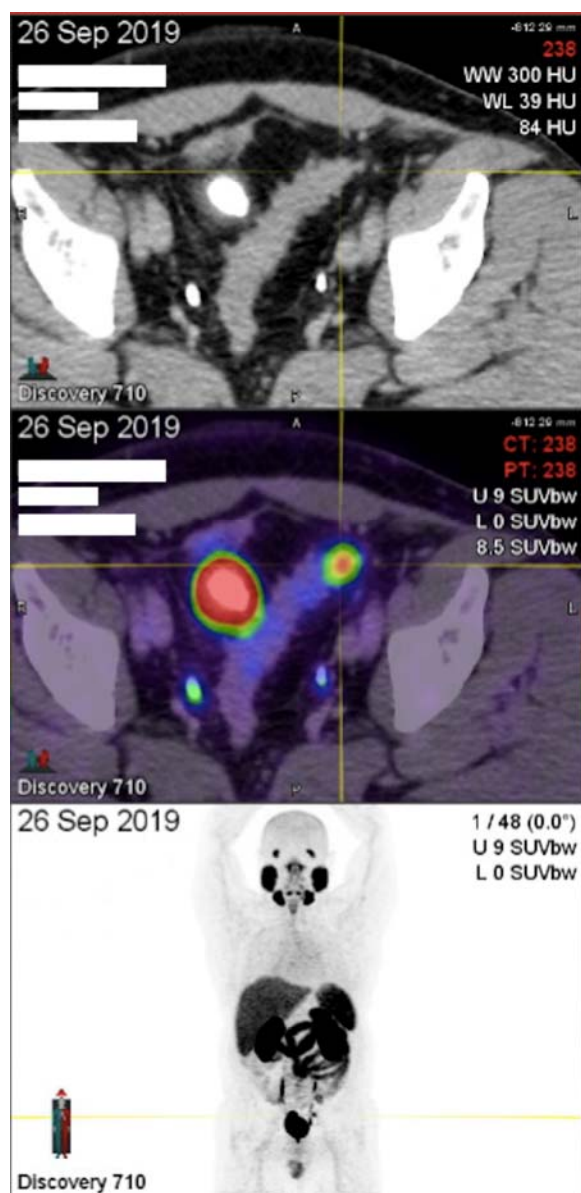
Fig. 2. Prostate-specific membrane antigen positron emission tomography/computed tomography for Case 3 demonstrating pathological uptake in subcutaneous lesion in the midline.
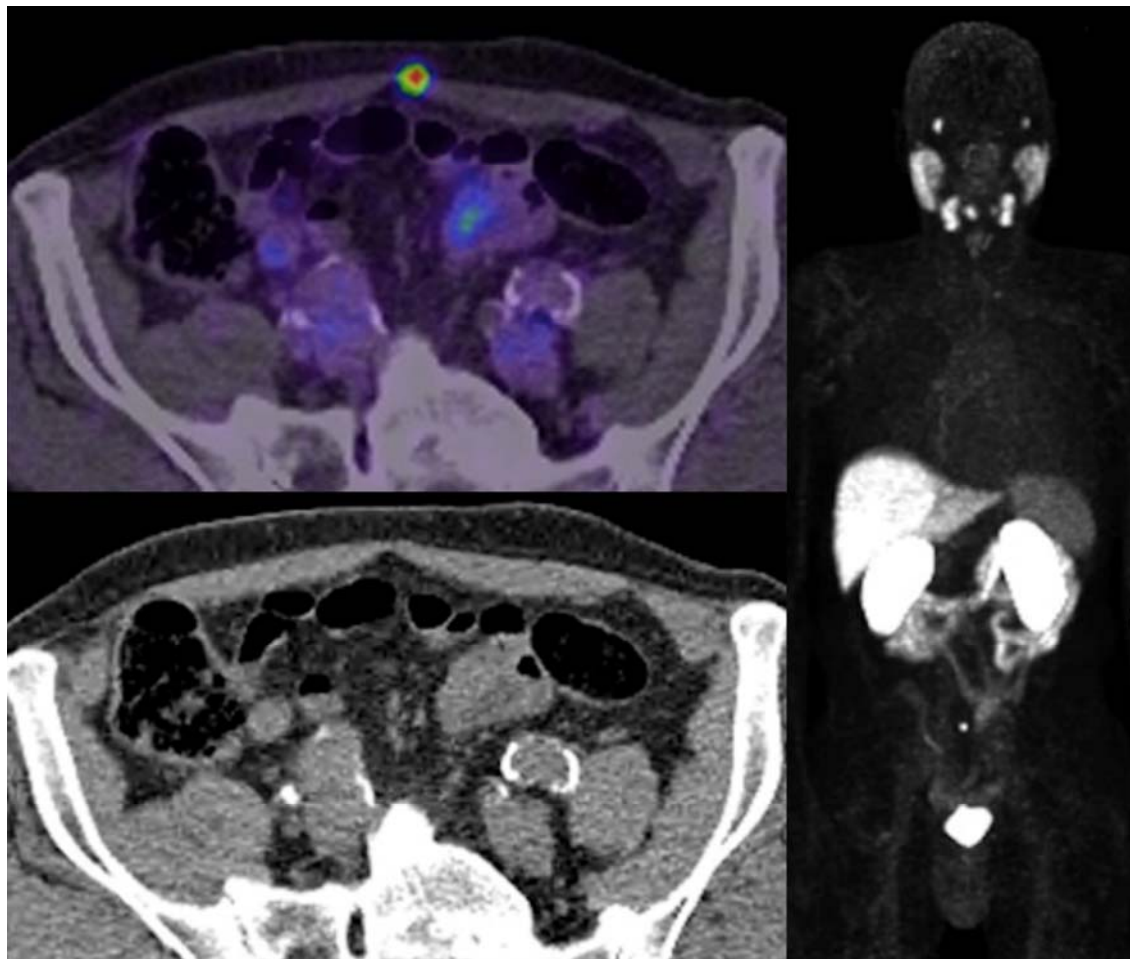
Table 1. Biochemical and histological characteristics of case series				
Patient	**Case 1**	**Case 2**	**Case 3**	**Case 4**
Initial PSA	4.2	5.6	13.13	12
Gleason score	5+4=9	3+4=7	4+5=9	4+5=9
TNM	T3bN0M0	pT4N0M0	T3aN0M0	T3aN0M0
Positive margin	Y	Y	Y	Y
EPE	Y	Y	Y	Y
Seminal vesicle involvement	Y	Not identified	N	N
LVI	N	Y	Y	N
PNI	Y	Y	Y	Y
Histology	Adenocarcinoma	Small cell carcinoma	Adenocarcinoma, some regions of intra-ductal	Ductal
Post-RARP PSA nadir	1.25	Unknown	<0.05	0.81
PSA at recurrence	6.1	Unknown	0.54	445
Current PSA	0.10	N/A	<0.03	N/A

LVI: lymphovascular invasion; PNI: perineural invasion; PSA: prostate-specific antigen;
RARP: robotic-assisted radical prostatectomy.

Table 2. Characteristics of reported cases in the literature with comparison to present case series

Author	Age	Initial PSA	Gleason score	TNM	Initial treatment	Interval to metastases (months)	Location	PSA at recurrence	Treatment of recurrence	Outcome
Acar et al[4]	66	6.8	4+5	T3aN0M0 + margin	RARP	21	Right hand port site	0.67	Continued ADT, surgical resection, abiraterone, scheduled chemotherapy	Rising PSA, further peritoneal carcinomatosis at 7 months, ongoing chemotherapy
Baber et al[5]	65	4.4	3+4	T2cN0M0	RARP	132	Widespread peritoneal carcinomatosis	6.6	ADT and abiraterone	Commencing chemotherapy at 3 months
Baber et al[5]	65	2.7	4+5	T3bN0M0	RARP	24	Mesenteric and pulmonary nodules	93.9	ADT, docetaxel, mitoxantrone, cabazitaxel	Transitioned to palliative care at 6 months
Bruyne et al[6]	46	32.8	4+3	T3bN0M0	RARP + salvage RTx	54	Left flank port-site + Inguinal lymph node	10.15	Surgical resection	PSA 0.09 at 1 month
Jundt et al[7]	57	Unknown	4+3	T2aN0M0	RARP + salvage RTx	60	Right rectus abdominis muscle	1.5	ADT and chemotherapy	Undetectable PSA following 6 cycles chemotherapy

Sheng et al[8]	60	9.5	3+4	Unknown	RARP + salvage RTx	29	Omentum	11.8	ADT, surgical resection, abiraterone	Peritoneal and lymph node recurrence following resection, ongoing chermotherapy.
Shin et al[9]	75	10.5	4+3	T3aN0M0 + margin	RARP	24	Liver and peritoneum	12.37	Surgical resection	Unknown
Calderoni et al[10]	67	8.2	4+3	pT2c	RARP + salvage RTx	37	Left-hand port site	0.98	Surgical resection	PSA 0.19 at 1 month
Case 1	62	4.2	5+4	T3bN0M0 + margin	EBRT + salvage RARP	5	Omentum and terminal ileum	6.1	Surgical resection	PSA 0.10 at 10 months on ADT
Case 2	71	5.6	3+4	T4N0M0 + margin	Robotic cysto-prostatectomy	3	Peritoneum	Unknown	Surgical resection	Deceased at 3 months from disease progression
Case 3	69	13.13	4+5	T3aN0M0 + margin	RARP + salvage RTx	96	Midline port site	0.54	Surgical resection	Undetectable PSA at 6 months
Case 4	67	12	4+5	T3aN0M0 + margin	RARP + salvage RTx	7	Peritoneum and omentum	445	ADT and chemotherapy	Deceased at 3 years from disease progression

ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; PSA: prostate-specific antigen; RARP: robotic-assisted radical prostatectomy.