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Tumour Seeding in the Tract of Percutaneous Renal Tumour Biopsy: A Report on Seven Cases from a UK Tertiary Referral Centre

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Abstract

The role of percutaneous renal tumour biopsy (RTB) in the management of radiological indeterminate renal masses is long established. Patients with small renal masses who have biopsy-proven renal cell carcinoma (RCC) may be offered surgery, ablative therapy, or active surveillance, and RTB can provide diagnostic tissue from patients with metastatic disease who might benefit from systemic therapy. Current guidelines suggest that tumour seeding along the needle tract is anecdotal, but several cases have been reported recently, although some have been associated with lack of a coaxial sheath. We report on seven patients who underwent surgical resection of RCC in our tertiary referral institution following diagnostic RTB between 2014 and 2017 for whom RTB tract seeding by tumour was identified on histological examination of the resection specimen. One of these patients subsequently developed local tumour recurrence at the site of the previous biopsy.

1. Case series

1.1. Background

The incidence of renal cell carcinoma (RCC) is rising, in part because of greater use of cross-sectional imaging and the resultant detection of incidental, small renal masses [1]. Some 20% of renal masses of <4 cm in diameter are benign [2] and renal tumour biopsy (RTB) can better characterise the nature of such lesions and help in determining appropriate management [3]. Patients with small renal masses who have biopsy-proven RCC may be offered surgery, ablative therapy (cryoablation or radiofrequency ablation), or active surveillance. Furthermore, RTB can provide diagnostic tissue from patients with metastatic disease who might be candidates for systemic therapy. During the procedure, the biopsy needle traverses skin, subcutaneous fat, multiple musculofascial layers, and perinephric fat before penetrating the renal mass; the tumour could theoretically seed into any of these tissues. Owing to this concern, use of a coaxial technique is recommended since it permits multiple passes through the lesion with only one pass through the adjacent normal tissue; this theoretically reduces the risk of needle tract seeding and may reduce patient discomfort [4].

The European Association of Urology guidelines suggest that tumour seeding of the RTB tract is anecdotal [5]; indeed, the risk of tumour seeding for all abdominal biopsies has been reported to be less than 1:10 000 [6]. However, several cases of RTB tract seeding have recently been reported, although some have been associated with lack of a coaxial sheath. Here we report on a series of seven patients who underwent surgical resection of RCC in our tertiary referral institution following diagnostic RTB for whom RTB tract seeding by tumour was identified on histological examination of the resection specimen.

1.2. Cases

Between January 2014 and November 2017, 585 renal tumour resections were performed at our institution, 218 of which were partial nephrectomies. In the same period, we performed 173 RTBs. Seven patients who underwent partial nephrectomy following diagnostic RTB (age 44–74 yr; 5 males, 2 females) were found to have tumour seeding of the RTB tract within the perinephric fat on histological assessment of the resection specimen (Table 1 and Figs. 1–3). Two RTBs were performed locally and the rest across several referring hospitals. We could find complete details of the biopsy procedure for five cases and partial details for two; an 18G needle with a coaxial technique was used in all cases for which these data are available (Table 2). Six tumours were papillary RCC (PRCC) and one was clear cell RCC (CCRCC). In four cases the site of the biopsy tract was suspected macroscopically as an area of fat necrosis or haemorrhage within the perinephric fat. In six cases the presence of tumour within the perinephric fat resulted in upstaging of the tumour, which would have otherwise been pT1 (Union for International Cancer Control TNM classification of malignant tumours, 8th edition). One of the patients subsequently developed local recurrence of the tumour within the renal bed at a site consistent with the biopsy tract (Fig. 4).

2. Discussion

This study represents the largest reported series of RTB tract seeding in which the cases were confirmed on histological examination of the resection specimen. In the modern literature, six cases of histologically proven RTB tract seeding have been reported (Table 3) [7–12], one of which was associated with histologically proven local recurrences within the biopsy tract, abdominal wall, and psoas muscle [12]. The majority of these cases were also PRCC, although the RCC subtype was not documented in the case with local recurrence. Use of a coaxial sheath was documented in only two cases [9,11]. In addition, four further cases of suspected RTB tract seeding (ie, not identified histologically within the resection specimen) and local recurrence have been reported [11–14]. Another case of cutaneous seeding after biopsy of a pulmonary CCRCC metastasis has been reported [15] and, more recently, a case of suspected seeding of a perinephric haematoma following RTB with subsequent local recurrence and metastatic disease has been published [16].

Over recent years there has been an increase in the use of RTB and it is likely that this will rise further, as tissue is required for diagnosis and assessment of biomarker status in the era of personalised medicine. This series challenges the widely documented rarity of RTB tract seeding; the cumulative incidence in our own institution over the period of this series is 1.2% (2/173) which, although still low, is significantly higher than published rates. Of the locally performed RTBs, 16 were reported as PRCC on biopsy, with two exhibiting seeding in the RTB tract (12.5% in our series). However, we are unable to determine the incidence of RTB tract seeding in patients who underwent ablation of their renal mass as opposed to surgical excision, since no postprocedure specimen is available for histological assessment. Furthermore, we also acknowledge that we are unable to provide the total number of RTBs performed across our referring institutions. Thus, we cannot specify an exact incidence of

RTB tract seeding in this wider patient cohort; given the referral nature of our practice, these data are not easily ascertained.

A recent study reviewed the National Cancer Data Base (2010–2013, USA and Puerto Rico) to identify patients with clinical pT1a tumours that were subsequently upstaged to pT3a on the basis of perinephric fat invasion identified within the surgical resection specimen [17]. Overall, 1.2% of patients were upstaged, but a subanalysis revealed that the rate of upstaging was 2.1% among patients who had undergone RTB versus 1.1% among those who had not (odds ratio 1.69, 95% confidence interval 1.17–2.44; $p < 0.01$). Furthermore, upstaging was associated with poorer overall survival (irrespective of whether or not a patient had undergone RTB). The authors acknowledge the lack of histological evidence as to whether perinephric fat invasion in the RTB cases was related to the site of prior biopsy or was present away from this area and, therefore true biological stage pT3a. However, it is interesting that the overall figures suggested in this study for RTB-associated upstaging are similar to those observed in our own small series of cases.

While we acknowledge that the incidence of RTB tract seeding is low and that its clinical significance has yet to be fully established, we also feel that it is important that there is greater awareness of the potential risk of seeding among clinicians managing patients with renal masses, including pathologists reporting on postbiopsy renal tumour resections. There was clear microscopic evidence of the site of a previous biopsy tract in each of the surgical resection specimens in our series and it was in these areas that the presence of tumour seeding was identified. Indeed, these specimens did not show tumour infiltration of perinephric fat away from the biopsy site. Having encountered the first couple of cases showing biopsy tract seeding, our pathologists scrutinised such areas during microscopic examination of postbiopsy resection specimens. Furthermore, it was recognised that sampling of areas in the resection specimen that showed macroscopic features suggestive of a biopsy tract (such as fat necrosis, haemorrhage, and fibrosis in the perinephric fat, and haemorrhagic foci in the capsular tissue) was important if biopsy tract seeding was to be identified. It is possible that most cases of biopsy tract seeding are being missed by pathologists as a result of failure to identify and adequately sample the site of a previous biopsy in tumour resection specimens. The clinical, radiological, and pathological data available in this small series are heterogeneous and no obvious risk factors for seeding emerge from these, other than biopsy of PRCC. Several potential technical risk factors for biopsy tract seeding have been proposed [18] but in our small series we have not demonstrated any particular aspect of biopsy technique that is associated with seeding. In the review of the National Cancer Database by Salmasi and colleagues [17], among other tumour-related and non-tumour-related factors, a diagnosis of PRCC or chromophobe RCC emerged as a predictor of perinephric fat spread. Interestingly, several studies have reported that both PRCC and chromophobe RCCs have less well-developed peritumoural pseudocapsules than CCRCCs, and that PRCCs more often demonstrate invasion beyond this layer [19–21]. Thus, it is possible that these observations may provide some biological explanation for the apparent propensity for seeding of PRCC in comparison to other RCC subtypes, as has been noted in the current series and other published reports. The recognition of cases of RTB tract seeding by tumour has changed pathological practice at our institution and in all likelihood we feel that the greatest factor contributing to the number of cases in our centre is that the pathologists recognised RTB seeding in the index case and were then more aware of the macroscopic and microscopic features to look for in subsequent cases. Our pathologists have been aided by the inclusion of details of the prior RTB on the surgical request form that accompanies each resection specimen; this is particularly important for patients who have undergone RTB elsewhere and therefore have no local pathology records. One of the patients in our series subsequently developed a local recurrence at the site of a prior diagnostic biopsy but we do not know the

number of patients with evidence of local recurrence on imaging associated with a prior RTB during the same period (ie, among patients who did not proceed to surgery or in whom seeding was not detected on pathological assessment).

The exact clinical significance of the presence of tumour within the perinephric fat when it is limited to the site of a previous RTB and fully excised at surgery is currently unclear.

Instinctively, it seems unlikely that this has the same prognostic implications as a stage pT3a tumour not showing RTB tract seeding. In spite of this, recognition of this condition may have implications for patient follow-up given that we now appreciate that these patients appear to be at risk of local recurrence. Thus, the utility of the information gained from RTB must be balanced against the small but real risk of seeding when deciding on the best course of action for patients presenting with renal masses.

Conflicts of interest: The authors have nothing to disclose.

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References

1. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer* 2008;113:78–83.
2. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. *J Urol* 2003;170:2217–20.
3. Phé V, Yates DR, Renard-Penna R, Cussenot O, Roupôt M. Is there a contemporary role for percutaneous needle biopsy in the era of small renal masses? *BJU Int* 2012;109:867–72.
4. Volpe A, Kachura JR, Geddie WR, et al. Techniques, safety and accuracy of sampling of renal tumors by fine needle aspiration and core biopsy. *J Urol* 2007;178:379–86.
5. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol* 2015;67:913–24.
6. Smith EH. Complications of percutaneous abdominal fine-needle biopsy. Review. *Radiology* 1991;178:253–8.
7. Mullins JK, Rodriguez R. Renal cell carcinoma seeding of a percutaneous biopsy tract. *Can Urol Assoc J* 2013;7:E176–9.
8. Laird A, Couper CH, Glancy S, O'Donnell M, Riddick AC. Renal cell carcinoma needle biopsy: sowing the seed for later complications? *BMJ Case Rep* 2014;2014:bcr2014203691.
9. Soares D, Ahmadi N, Crainic O, Boulas J. Papillary renal cell carcinoma seeding along a percutaneous biopsy tract. *Case Rep Urol* 2015;2015:925254.
10. Chang DT, Sur H, Lozinskiy M, Wallace DM. Needle tract seeding following percutaneous biopsy of renal cell carcinoma. *Korean J Urol* 2015;56:666–9.
11. Viswanathan A, Ingimarsson JP, Seigne JD, Schned AR. A single-centre experience with tumour tract seeding associated with needle manipulation of renal cell carcinomas. *Can Urol Assoc J* 2015;9:E890–3.
12. Andersen MF, Norus TP. Tumor seeding with renal cell carcinoma after renal biopsy. *Urol Case Rep* 2016;9:43–4.

13. Giordadze T, Qureshi F, Aulicino M, Jacques SM. Retroperitoneal recurrence of a stage 1 renal cell carcinoma four years following core biopsy and fine needle aspiration: possible needle tract seeding. *Diagn Cytopathol* 2013;41:470–2.
14. Sainani NI, Tatli S, Anthony SG, Shyn PB, Tuncali K, Silverman SG. Successful percutaneous radiologic management of renal cell carcinoma tumor seeding caused by percutaneous biopsy performed before ablation. *J Vasc Interv Radiol* 2013;24:1404–8.
15. Jilani G, Mohamed D, Wadia H, et al. Cutaneous metastasis of renal cell carcinoma through percutaneous fine needle aspiration biopsy: case report. *Dermatol Online J* 2010;16(2):10.
16. Caputo C, Lee Z, Harbin A, Eun D. Renal cell carcinoma metastasis from biopsy associated hematoma disruption during robotic partial nephrectomy. *Case Rep Urol* 2014;2014:975412.
17. Salmasi A, Faiena I, Lenis AT, et al. Association between renal mass biopsy and upstaging to perinephric fat involvement in a contemporary cohort of patients with clinical T1a renal cell carcinoma. *Urol Oncol*. In press.
<http://dx.doi.org/10.1016/j.urolonc.2018.08.009>
18. Tyagi R, Dey P. Needle tract seeding: an avoidable complication. *Diagn Cytopathol* 2014;42:636–40.
19. Roquero L, Kryvenko ON, Gupta NS, Lee MW. Characterization of fibromuscular pseudocapsule in renal cell carcinoma. *Int J Surg Pathol* 2015;23:359–63.
20. Jacob JM, Williamson SR, Gondim DD, et al. Characteristics of the peritumoral pseudocapsule vary predictably with histologic subtype of T1 renal neoplasms. *Urology* 2015;86:956–61.
21. Snarskis C, Calaway AC, Wang L, et al. Standardized reporting of microscopic renal tumor margins: introduction of the renal tumor capsule invasion scoring system. *J Urol* 2017;197:23–30.

Fig. 1 – Macroscopic findings for case 2. The main image shows areas of haemorrhage within the renal capsule (circled) with tiny foci of fat necrosis present in the overlying perinephric fat. There was a large area of haemorrhage within the tumour (top right) that was confirmed microscopically (bottom right). The haemorrhagic area corresponded to the site of the biopsy (Fig. 2).

Fig. 2 – Microscopic findings for case 2. Within the area of macroscopically abnormal perinephric fat sampled there were dispersed, tiny foci of tumour present (arrows) in association with fat necrosis, fibrosis, haemosiderin deposition, and a foreign body reaction to cholesterol (haematoxylin and eosin stain; low magnification top left, high magnification top right). The tumour foci were confirmed immunohistochemically using CK7 (bottom left) and PAX8 (bottom right). The speckled light brown/gold pigment is haemosiderin.

Fig. 3 – Microscopic findings for case 1. Renal tumour seeding of the biopsy tract with clear cell renal cell carcinoma was an incidental finding within the perinephric fat sampled (haematoxylin and eosin stain; low magnification left, high magnification right). The tumour was present within fibrous tissue showing features in keeping with the biopsy site and was discontinuous with the main tumour.

Fig. 4 – Radiological evidence of tumour recurrence from case 1 (transaxial arterial phase computed tomography images with tumours highlighted in red). A preoperative

image (left) demonstrates a tumour within a solitary left kidney. Postoperative images demonstrate a centrally located renal recurrence (middle) and a second, separate recurrence within the renal bed (right). The central recurrence represents tumour within the renal sinus fat related to the positive nephric margin at initial surgery, whereas the second recurrence is at the site of the previous renal tumour biopsy tract.

CME question

To date, which subtype of renal cell carcinoma has been most associated with renal tumour biopsy tract seeding?

- A. Clear cell renal cell carcinoma
- B. Papillary renal cell carcinoma
- C. Chromophobe renal cell carcinoma
- D. Collecting duct renal cell carcinoma

CME answer

- B. Papillary renal cell carcinoma

Table 1 – Clinicopathological details for this case series

Case	Patient		Surgical procedure	Tumour size ^a (cm)	Biopsy site noted macroscopically in resection specimen?	RCC subtype ^b	Tumour stage ^c	Tumour upstaged due to biopsy tract seeding?	Additional prognostic histological features	Local recurrence?
	Age (yr)	Gender								
1	66	F	Open PN (left)	5.4	No	CCRCC (Fig. 3)	pT3a	No; already stage pT3a due to sinus vein invasion	ISUP grade 4, tumour necrosis present, no sarcomatoid or thabddoid change; Leibovich score = 8, PNM	Yes; local recurrences at two separate sites at 24 mo, one considered related to RTB site and the other at the site of the PNM (Fig. 4) Patient has since died of metastatic disease
2	73	M	Open PN (left)	5.8	Yes; areas of haemorrhage into the capsular surface of the PNF and tiny foci of fat necrosis within the adjacent fat (Fig. 1)	PRCC (type 1; Fig. 2)	pT3a	Yes	ISUP grade 3, tumour necrosis present, no sarcomatoid or thabddoid change; NNM	No; free of recurrence at last follow-up (12 mo) Patient has since died of unrelated causes
3	44	M	Open PN (left)	4.6	No	PRCC (type 2)	pT3a	Yes	ISUP grade 3, tumour necrosis present, no sarcomatoid or thabddoid change; NNM	No; free of recurrence at last follow-up (36 mo)
4	71	F	Robot-assisted laparoscopic PN (right)	2.7	Yes; areas of haemorrhage into the capsular surface of the PNF	PRCC (type 1)	pT3a	Yes	ISUP grade 3; no tumour necrosis, no sarcomatoid or thabddoid change; NNM	No; free of recurrence at last follow-up (18 mo)
5	49	M	Robot-assisted laparoscopic PN (left)	2.0	Yes; fat necrosis within the PNF, extending to the surgical margin in this area, and breach of the renal capsule	PRCC (type 1)	pT3a	Yes	ISUP grade 3, tumour necrosis present, no sarcomatoid or thabddoid change; PNM	No; free of recurrence at last follow-up (9 mo)
6	60	M	Robot-assisted laparoscopic PN (right)	5.0	Yes; yellowish areas noted in the PNF (haemosiderin microscopically)	PRCC (type 1 + some type 2 areas)	pT3a	Yes	ISUP grade 3, tumour necrosis present, no sarcomatoid or thabddoid change; NNM	No; free of recurrence at last follow-up (11 mo)
7	74	M	Open PN (left)	2.7	No	PRCC (type 1)	pT3a	Yes	ISUP grade 2; no tumour necrosis, no sarcomatoid or thabddoid	No; free of recurrence at last follow-up (6 mo)

CCRCC =clear cell RCC; F = female; ISUP – International Society of Urological Pathology; M = male; NNM = negative nephric margin; PN = partial nephrectomy; PNF = perinephric fat; PNM = positive nephric margin; PRCC = papillary RCC; RCC = renal cell carcinoma; RTB = renal tumour biopsy.

^a From resection specimen.

^b World Health Organisation 2016 classification.

^c According to Union for International Cancer Control TNM 8th edition.

Table 2 – Technical details of the biopsies performed in this case series

Case	Needle size (G)	Coaxial technique used	Biopsy attempts (<i>n</i>)	Tissue cores taken (<i>n</i>)	Diagnostic biopsy	Postbiopsy complications
1	18	Yes	1	Unknown	Yes	No
2	Unknown	Unknown	1	2	Yes	Bleeding at the time of biopsy
3	18	Yes	1	3	Yes	No
4	18	Yes	1	2	Yes	No
5	18	Yes	1	2	Yes	No
6	18	Yes	1	4	Yes	No
7	18	Yes	1	4	Yes	No

Table 3 – Previous reports of histologically evident renal tumour biopsy tract seeding

Study	Patient details	RCC subtype	Location of spread	Needle size (G)	Coaxial technique
Mullins and Rodriguez (2013) USA [7]	68yo M; incidental 4.7-cm left renal cyst	PRCC (type NR)	Perinephric fat	20 (core biopsy) 22 (FNA)	No
Laird et al (2014) UK [8]	58yo M; incidental 2.4-cm left kidney mass	PRCC (type 1)	Perinephric fat	18 (core biopsy)	No
Soares et al (2015) Australia [9]	50yo M; incidental 2.6-cm left kidney mass	PRCC (type 1)	Perinephric fat	17 (core biopsy + FNA) 18 (core biopsy)	Yes
Chang et al (2015) Australia [10]	66yo M; incidental 3.2-cm right kidney mass	CCRCC	Perinephric fat	16 and 22 (core biopsy)	No
Viswanathan et al (2015) USA [11]	53yo M; haematuria and 0.8-cm right kidney mass	PRCC (type 1)	Perinephric fat	20 (core biopsy)	Yes
Andersen and Norus (2016) Denmark [12]	60yo F; haematuria and small right kidney mass	RCC (subtype NR)	Perinephric fat and subsequent multiple recurrences in abdominal wall	NR (core biopsy)	NR

CCRCC = clear cell RCC; F = female; FNA = fine needle aspiration; M = male; NR = not reported; PRCC = papillary RCC; RCC = renal cell carcinoma; yo = year-old.

Figure 1

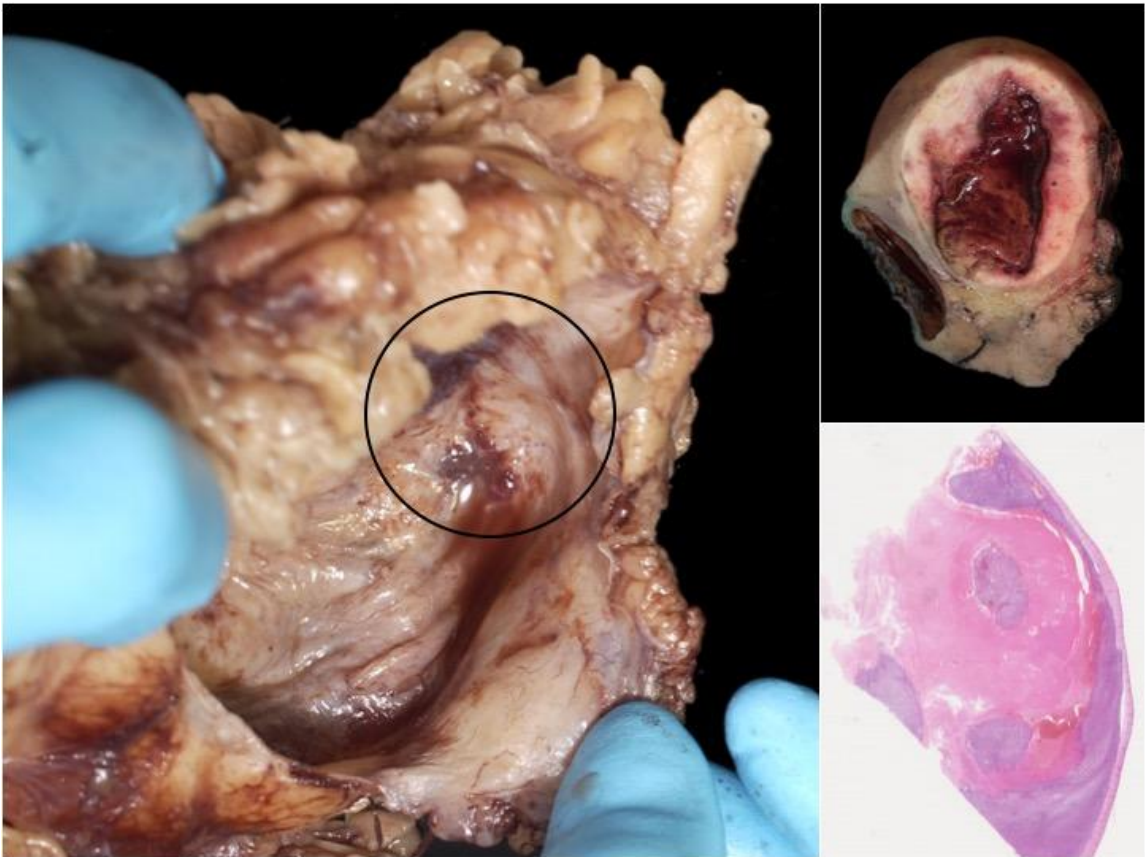


Figure 2

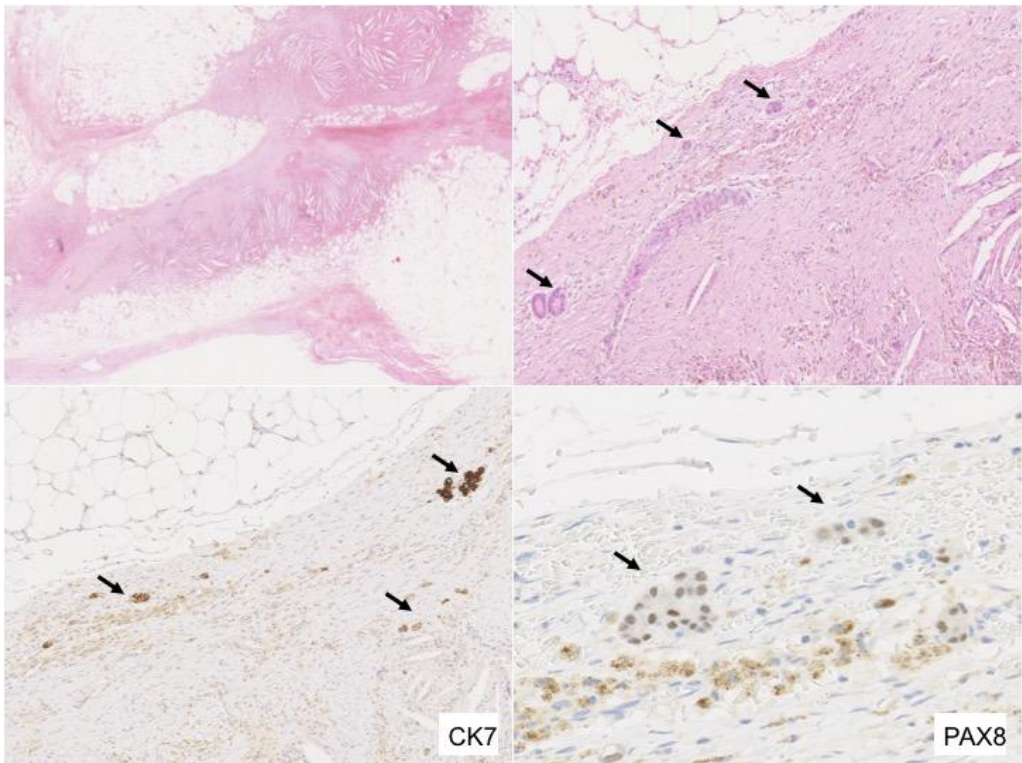


Figure 3

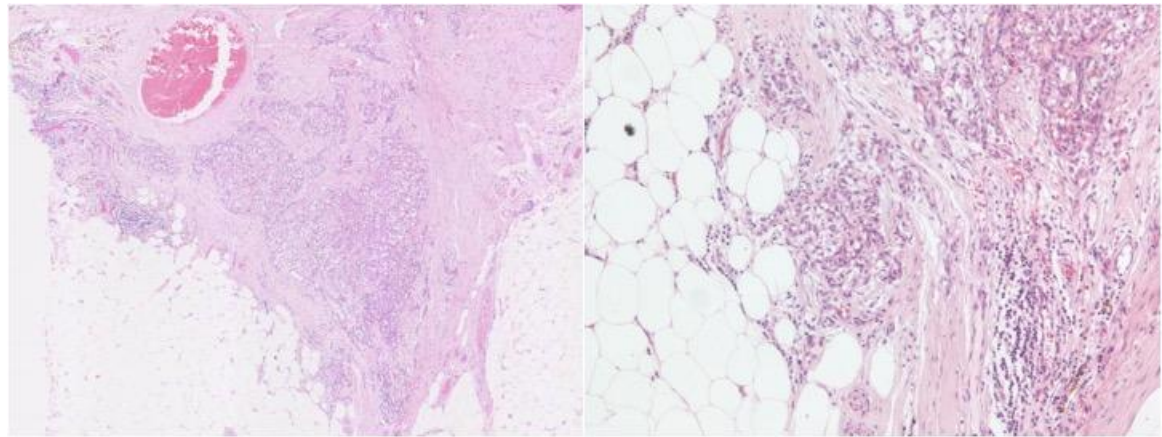


Figure 4

