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Correlation between percutaneous biopsy and final histopathology for retroperitoneal sarcoma: A single-centre study

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Abstract

Background:

Retroperitoneal sarcomas are rare soft tissue tumours accounting for 10-15% of soft tissue sarcomas. Patient prognosis and treatment recommendations (including extent of surgery and neoadjuvant strategies) are determined by the preoperative histopathological subtype and grade obtained from biopsy and thus it is important to understand the accuracy of biopsy in retroperitoneal masses.

Materials and methods: This study presents a case series of primary retroperitoneal sarcomas managed at Peter MacCallum Cancer Centre (PMCC) between 2008 and 2019. Statistical analyses were performed to determine correlation between histopathology from percutaneous biopsy and surgical excision.

Results: A total of 117 patients who underwent percutaneous core biopsy and surgical excision of retroperitoneal sarcoma were included. Diagnostic accuracy varied with histopathological diagnosis, but overall precise concordance between biopsy and final histopathology was seen in 61% (κ = 0.57). Biopsy was most sensitive for identifying well differentiated liposarcoma (WDLPS) (sensitivity 85%, 95% CI 0.06 to 0.96) and leiomyosarcoma (sensitivity 81%, 95% CI 0.54 to 0.96) and was least sensitive for identifying dedifferentiated liposarcoma (DDLPS) (sensitivity 40%, 95% CI 0.25-0.56). Overall agreement between biopsy and final histopathology increased with use of PET/CT scan pre-biopsy and with use of FISH testing on biopsy, however, neither test improved recognition of dedifferentiated components within WD/DDLPS on core biopsy.

Conclusions:

Pre-operative biopsy is important for clinical decision making in the treatment of retroperitoneal sarcoma. A significant portion of patients with a WDLPS will have a dedifferentiated component identified at the time of resection that was not identified on initial biopsy.

Introduction

The retroperitoneum is the site of origin for approximately 10-15% of all soft tissue sarcomas with an incidence between 0.5-1 new diagnoses per 100,000 population per year[1]. The primary treatment modality for the majority of patients is surgical resection, with radiotherapy or chemotherapy being selectively used in the adjuvant/neoadjuvant setting[2]. The differential diagnosis for retroperitoneal masses is broad and includes over 70 subtypes of retroperitoneal sarcoma (RPS) as well as a host of non-sarcomatous malignancies and a number of benign masses[1, 3]. Patient prognosis and treatment recommendations (including extent of surgery and neoadjuvant strategies) are determined by the preoperative histopathological subtype and grade obtained from biopsy of a retroperitoneal mass and thus thorough pre-operative workup is required. Liposarcoma (LPS) is the most common type of soft tissue sarcoma overall and the most common pathological type of sarcoma occurring in the retroperitoneum. Liposarcoma can be further classified into four histologic subtypes – well differentiated (WDLPS), well differentiated/de-differentiated (WD/DDLPS), myxoid and pleomorphic types[4-6]. For patients with WD/DDLPS, the presence of a de-differentiated component and its grade are the most important prognostic factors with the de-differentiated component associated with an increased risk of recurrence and mortality[7].

Definitive diagnosis of retroperitoneal masses can be difficult to achieve radiologically and thus percutaneous biopsy is recommended to guide diagnosis and

treatment[2]. The extent of dedifferentiation in a WD/DDLPS is variable and heterogeneous and therefore, even when the diagnosis of sarcoma is made, sampling error from biopsy may result in incorrect subtype-specific diagnosis or inaccurate tumour grading.

Given the heavy reliance on pre-operative biopsy in determining management plans, it is important to establish the accuracy of percutaneous core biopsy for determining histopathology of retroperitoneal sarcomas. The aim of this study was to assess the accuracy of percutaneous biopsy for predicting final histopathological subtype for retroperitoneal sarcomas in an Australian specialist sarcoma centre and to comment on whether adjunct tests such as positron emission tomography/computed tomography (PET/CT) scan or fluorescence in situ hybridisation (FISH) testing improve diagnostic accuracy.

Materials and Methods

This study presents a case series of primary retroperitoneal sarcoma cases managed at the Peter MacCallum Cancer Centre (PMCC) between 2008 and 2019. Patients who underwent both percutaneous core biopsy and surgical resection of a retroperitoneal mass with the histopathology of one or both of these interventions suggesting a diagnosis of retroperitoneal sarcoma were included in this study.

Patients were excluded if no pre-operative biopsy was undertaken or if an alternative biopsy technique was utilised.

Percutaneous biopsies were undertaken under radiological guidance by specialist interventional radiologists with extensive experience in sarcoma at an external site and all histopathology was reviewed by pathologists with specialisation in sarcoma. As part of standard practice, the imaging, histopathology and management of patients receiving treatment through PMCC was discussed at a sarcoma multidisciplinary meeting.

This paper classified biopsy and final histopathology results as either well-differentiated liposarcoma (WDLPS), well differentiated/de-differentiated liposarcoma (WD/DDLPS), leiomyosarcoma (LMS), myxoid liposarcoma (myxoid LPS), undifferentiated pleomorphic sarcoma (UPS), solitary fibrous tumour (SFT), other sarcoma, non-sarcoma malignancy, benign tumour or non-diagnostic.

Data were extracted from hospital files prior to 2016 and then from a prospectively maintained registry of retroperitoneal sarcoma patients thereafter (2016-2019). Data pertaining to demographics, percutaneous biopsy results, pre-operative radiological staging, specifications of surgical resection and post-operative histopathology were collected for each patient.

Percutaneous biopsy results were compared with final histopathology from surgical resection using a Clopper-Pearson exact test to calculate 95% confidence intervals (CIs). Diagnostic performance was described by sensitivity, specificity, positive and negative predictive value (PPV and NPV). A weighted kappa statistics (κ) with 95% CIs was used to assess agreement between biopsy and final histopathology; $\kappa \leq 0$ interpreted as no agreement, κ=0.01 to 0.2 as none to slight, κ =0.21 to 0.4 as fair, κ =0.41 to 0.60 as moderate, κ =0.61 to 0.80 as substantial, and κ =0.81-1.00 as almost perfect agreement[4] (see table 1).

Ethical approval for this project was obtained from the Human Resources and Ethics Committee (HREC) at PMCC. Data were anonymised at the time of collection and stored in accordance with the HREC specifications.

Results

A total of 117 patients who received care at PMCC between 2008 and 2019 were included in this study (see table 2). The majority of patients underwent surgical resection at PMCC, however 9 patients had their initial surgery at other centres. Forty-one percent (n=48) were female and the median age at diagnosis was 60 years old (range 18-86 years). Two patients had more than one biopsy undertaken due to non-diagnostic biopsy results.

Based on final surgical pathology, the diagnosis was WDLPS (22%, n=26), WD/DDLPS (37%, n=43), LMS (14%, n=16), myxoid LPS (2%, n=2), UPS (4%, n=5), SFT (9%, n=10), other sarcoma (6%, n=7) or a benign process (5%, n=6) (see table 3). Comparison between percutaneous biopsy and final histopathology from surgical resection was analysed based on histopathological subtype and sensitivity, specificity, positive and negative predictive values were calculated for each (see table 4). Biopsy accuracy varied with histopathological subtype, however, overall agreement between biopsy and final pathology was seen in 61% of cases (κ= 0.57, 95% CI 0.45 to 0.69).

Sensitivity was highest for myxoid liposarcoma (100%, 95% CI 0.16 to 1.00) followed by WDLPS (85%, 95% CI 0.65 to 0.96) and LMS (81%, 95% CI 0.54 to 0.96). Despite the high sensitivity, PPV for WDLPS was only 58% as 13 tumours that were initially biopsied as WDLPS were found to have a de-differentiated component on final histopathology. Sensitivity was lowest for detecting DDLPS (40%, 95% CI 0.25 to 0.56) and in 56% of cases where the initial biopsy was discordant with final histopathology, the final diagnosis was DDLPS (n=26). Despite the low sensitivity, the specificity of percutaneous biopsy for DDLPS was high (92%, 95% CI 0.83 to 0.97) demonstrating that when de-differentiation was identified on percutaneous biopsy, that this was likely to be a true finding.

Of the 26 cases of DDLPS that were not correctly diagnosed on percutaneous biopsy, half of these were initially thought to be WDLPS and the rest were either classified as UPS (23%), SFT (4%), indeterminate/other sarcoma (11.5%) or benign tumours (11.5%) on percutaneous biopsy. When considering liposarcoma as a single group therefore (WDLPS and WD/DDLPS together), sensitivity of percutaneous improved to 81% (95% CI 0.70 to 0.90) and specificity was 90% (95% CI 0.77 to 0.97).

Subgroup analysis

Subgroup analysis was undertaken according two main factors which may have impacted upon the concordance between percutaneous biopsy and final histopathology (see table 5). The first factor was use of PET/CT scan prior to biopsy and the second was use of fluorescence in-situ hybridisation testing on core biopsies.

PET/CT scan prior to biopsy

In this study, ^{18}F-fluorodeoxyglucose positron emission tomography / computed tomography (FDG-PET/CT) imaging was undertaken prior to percutaneous biopsy in 43% of cases (n=50). The agreement between biopsy and final pathology in those who underwent PET/CT scan prior to biopsy was substantial (κ=0.69, 95% CI 0.53 to 0.84) whilst for those who did not undergo PET/CT scan was moderate (κ=0.48, 95% CI 0.30 to 0.65). The sensitivity of biopsy for diagnosing WDLPS, DDLPS and

LPS combined was higher for all groups than when PET/CT was undertaken prior to biopsy however, despite biopsy sensitivity increasing, PPV for WDLPS remained low 59% (CI 0.36 to 0.79) suggesting that PET/CT did not improve the detection of de-differentiated components in WD/DDLPS.

Fluorescence In-Situ Hybridisation (FISH)

FISH testing for the MDM2 (murine double minute) gene was undertaken on percutaneous biopsies in 78 cases (67%). There was substantial agreement between biopsy and final pathology in those who had FISH testing undertaken on their biopsy (κ=0.77, CI 0.65 to 0.90) whilst fair agreement for those who did not have FISH testing undertaken (κ=0.25, CI 0.06 to 0.44). The main benefit of FISH testing is in identifying DDLPS from UPS with similar undifferentiated appearance histologically, but the presence of MDM2 amplification is diagnostic of DDLPS. It was noted that in 6 cases, patients were initially diagnosed with UPS on percutaneous biopsy and subsequently diagnosed with WD/DDLPS on final histopathology from surgical resection. None of these 6 cases had FISH testing undertaken on their percutaneous biopsies.

FISH and PET/CT combined

There were 33 cases where both PET/CT scan prior to biopsy and FISH were undertaken. These 33 cases demonstrated almost perfect agreement between biopsy and final pathology (κ=0.85, 95% CI 0.70 to 1.00). Of these 33 cases, the

sensitivity of biopsy for WDLPS was 100% (95% CI 0.66 to 1.00), for DDLPS the sensitivity was 60% (95% CI 0.32 to 0.84) and for LPS as a combined entity the sensitivity was 100% (95% CI 0.86 to 1.00). Even when both PET/CT and FISH were undertaken, there were still 7 cases where DDLPS was initially diagnosed as WDLPS and the PPV of WDLPS was unchanged (56%, CI 0.30 to 0.80). In the 6 cases in which DDLPS was initially diagnosed as UPS, no patients had both PET/CT and FISH undertaken.

Discussion

Retroperitoneal sarcoma is a rare and heterogenous diagnosis for which the mainstay of treatment remains surgical resection. Tumour behaviour varies depending on pathological subtype, and particularly, on histological grade and thus determining correct diagnosis is important for optimal prognostication and management. There are some studies assessing the accuracy of biopsy in diagnosing retroperitoneal sarcoma, but the published evidence still remains limited. The findings of this study however are in keeping with those already published in the broader literature. A recent paper by Almond et al[7] looking at diagnostic accuracy of percutaneous biopsy in retroperitoneal sarcoma at two major sarcoma centres in Europe reported an overall concordance rate of 67% (κ=0.60) for biopsy and final histopathology for retroperitoneal sarcomas. The subgroup analysis reported by Almond reported findings similar to this study with a sensitivity of 95% for WDLPS,

40% for DDLPS and 85% for LPS combined. Ikoma et al[8] similarly concluded that percutaneous biopsy had poor accuracy for correctly diagnosing DDLPS (36.5% vs 85.1% accuracy of diagnosing WDLPS).

There are several reasons as to why diagnosis of DDLPS is likely to be less accurate on percutaneous biopsy than other subtypes of sarcoma. DDLPS by nature is a heterogenous tumour type, characterised by the presence of de-differentiated tumour elements within a WDLPS. As such, sampling error may occur and lead to biopsies identifying only well-differentiated components, thus failing to diagnose DDLPS (see figure 1). Additionally, the de-differentiated tumour components can have variable morphology also and thus may be mistaken for other tissue diagnoses. Increasingly, adjunct diagnostic tools are being used to assist with increasing biopsy accuracy. Two particular diagnostic adjuncts at present are FDG-PET/CT scan and FISH testing for MDM2 gene amplification.

At PMCC, PET/CT scan is undertaken as a routine part of work up for patients with sarcoma (although as seen in this study, timing of PET/CT relative to biopsy can be inconsistent based on the scheduling availability with only 43% being undertaken prior to biopsy). FDG-PET/CT imaging provides high grade imaging of sarcomas and can be useful for providing an overall picture of heterogeneity in sarcoma tissues. Cells with a high metabolic activity (e.g. malignant or inflammatory cells) take up FDG to a greater extent than less active cells. Several studies report a positive

correlation between tumour grade and Standardised Uptake Value Maximum (SUVmax) suggesting that FDG-PET/CT may be useful for distinguishing between high and low grade sarcomas but it may not provide useful additional information for discriminating between benign pathologies and low grade soft tissue sarcomas[9-14]. The literature suggests that FDG-PET/CT SUVmax is a prognostic factor with increased SUVmax being associated with poorer overall survival and disease progression in sarcoma[15]. In theory, PET/CT scan may assist in improving accuracy of percutaneous biopsy by allowing clinicians to see and target the most metabolically active components of the tumour[15]. This study observed a small increase in the sensitivity of percutaneous biopsy across all sarcoma histologic subtypes when PET/CT scan was undertaken prior to biopsy. Despite the increase in sensitivity however, PET/CT did not assist with differentiating between WDLPS and DDLPS in this cohort. Notwithstanding the limitations of FDG-PET, this study suggests that PET scan may provide additional benefit in improving diagnostic accuracy and prognostic stratification in patients with RPS and therefore it should be considered in the management of patients with RPS and be scheduled prior to tumour biopsy.

Fluorescence in situ hybridisation (FISH) has increasingly been used to assist in diagnosis of RPS over the last 10 years. FISH is a cytogenetic test which utilises a fluorescent probe to identify the presence of specific gene sequences[16]. Amplification of the MDM2 gene is characteristic of WDLPS and WD/DDLPS and

can assist in differentiating these pathologies from other sarcomatous subtypes (e.g. pleomorphic sarcoma) or benign tumours with a similar morphological appearance such as renal angiomyolipoma[17-20]. As observed in this study, the sensitivity of biopsy for detecting LPS as a whole increased to 94% when FISH was undertaken on percutaneous biopsies. Interestingly however, in this study, a large number of the tumours that were incorrectly diagnosed on percutaneous biopsy were DDLPS that were initially diagnosed as WDLPS and thus FISH was not a useful test for distinguishing between these pathologies.

Myxoid liposarcoma is another sarcoma subtype in which molecular testing for genetic mutations can assist accurate diagnosis. Myxoid liposarcomas typically demonstrate abnormalities in the FUS-DDIT3 (fused in sarcoma) gene, and presence of such abnormalities can help to differentiate between myxoid liposarcoma and other tumours with a similar histological appearance[21]. In this study there were only four patients with a pre-operative diagnosis of myxoid liposarcoma. In two of these cases, the diagnosis was revised on final pathology (one received a final diagnosis of myoepithelial carcinoma and the other a diagnosis of myxofibrosarcoma). Neither of these cases underwent molecular testing on the initial biopsy specimen and occurred in the early period of the study cohort. These findings suggest that a pre-operative diagnosis of myxoid liposarcoma requires confirmatory molecular pathology (as is now routine at our institution).

An important component of the optimal multidisciplinary management of patients with a new diagnosis of suspected sarcoma is pathology review by an expert sarcoma pathologist. The NICE guidelines for management of sarcoma recommend that all patients with a suspected or confirmed diagnosis of sarcoma should have their care discussed at a specialist sarcoma multidisciplinary meeting[22, 23]. As part of this process, it is recommended that pre-operative biopsy is undertaken by a specialist with an interest in sarcoma management and that histopathology is reviewed by an expert pathologist. All patients with a suspected diagnosis of retroperitoneal sarcoma should be referred to a sarcoma specialist centre for review of imaging and confirmation of diagnosis via tissue biopsy. These patients should be reviewed at a sarcoma multidisciplinary meeting to obtain expert, consensus opinion about their management.

All patients with a suspected retroperitoneal sarcoma should have preoperative core needle biopsy to clarify the diagnosis and allow optimal therapy. The biopsy is important to rule out other (non-sarcoma) pathologies as well as to identify the histological subtype and grade of sarcoma. A limitation of this study is that the sampled population only included patients with a definitive diagnosis of RPS. As such, this study did not include patients with suspected RPS on imaging where the preoperative biopsy was benign or consistent with an alternative pathology. Future studies that include this population will provide a clear understanding of the utility of core biopsy in patients with suspected RPS.

Conclusion

Retroperitoneal sarcomas are a rare and heterogenous group of soft tissue tumours. Management of these tumours relies heavily on percutaneous core biopsy to guide treatment plans, however, the accuracy of biopsy results varies between histopathological subtypes of retroperitoneal sarcoma. A significant number of patients with a well differentiated liposarcoma will have a dedifferentiated component identified at the time of resection that was not identified on initial biopsy. While adjunct investigations such as pre-biopsy PET/CT scan and use of FISH testing on biopsies may improve biopsy sensitivity for subtypes of sarcoma, neither one improves the detection of dedifferentiated components on biopsy.

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Disclosure statement

The authors have no conflict of interest to disclose.

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Figure Legends

Figure 1: Case example of a retroperitoneal sarcoma where initial biopsy suggested a diagnosis of WDLPS with surgical resection specimen demonstrating 20% dedifferentiation making the final diagnosis WD/DDLPS

a) Pre-biopsy CT scan
b) Pre-biopsy PET scan
c) Surgical specimen

Table 1: Agreement between biopsy and final histopathology (Cohen's kappa)

Subgroup	Kappa score (95% CI)	Agreement
All	0.57 (0.45 to 0.69)	Moderate agreement
All subgroups with PET pre-biopsy	0.69 (0.53 to 0.84)	Substantial agreement
All subgroups without PET pre-biopsy	0.48 (0.30 to 0.65)	Moderate agreement
All subgroups with FISH on biopsy	0.77 (0.65 to 0.90)	Substantial agreement
All subgroups without FISH on biopsy	0.25 (0.06 to 0.44)	Fair agreement
All subgroups with both PET and FISH	0.85 (0.70 to 1.00)	Almost perfect agreement

Table 2: Demographics

Characteristic	Number
Sex Male Female	 69 (58.97%) 48 (41.03%)
Median age	60 years (range 18-86mm)
Median tumour size	142mm (range 23-380mm)
PET pre-biopsy Yes No	 49 (41.88%) 68 (58.12%)
FISH on biopsy Yes No Unknown	 78 (66.67%) 26 (22.22%) 13 (11.11%)
Neoadjuvant radiotherapy	85 (72.65%)

Table 3: Percutaneous biopsy and final histopathology

Biopsy result	Histopathology from surgical resection n (sensitivity %)										
	WDLPS	DDLPS	LMS	Myxoid LPS	UPS	SFT	Other sarcoma	non-sarcoma malignancy	benign tumour	non-diagnostic	Total
WDLPS	22 (85%)	13	0	0	0	1	0	0	2	0	38
DDLPS	4	17 (40%)	1	0	0	1	0	0	0	0	23
LMS	0	0	13 (81%)	0	0	0	0	0	0	0	13
Myxoid LPS	0	0	0	2 (100%)	0	0	1	1	0	0	4
UPS	0	6	1	0	2 (40%)	0	0	0	0	0	9
SFT	0	1	0	0	0	7 (70%)	0	0	0	0	8
Other sarcoma	0	3	0	0	1	0	4 (57%)	0	0	1	9
non-sarcoma malignancy	0	0	0	0	1	0	1	0	0	0	2

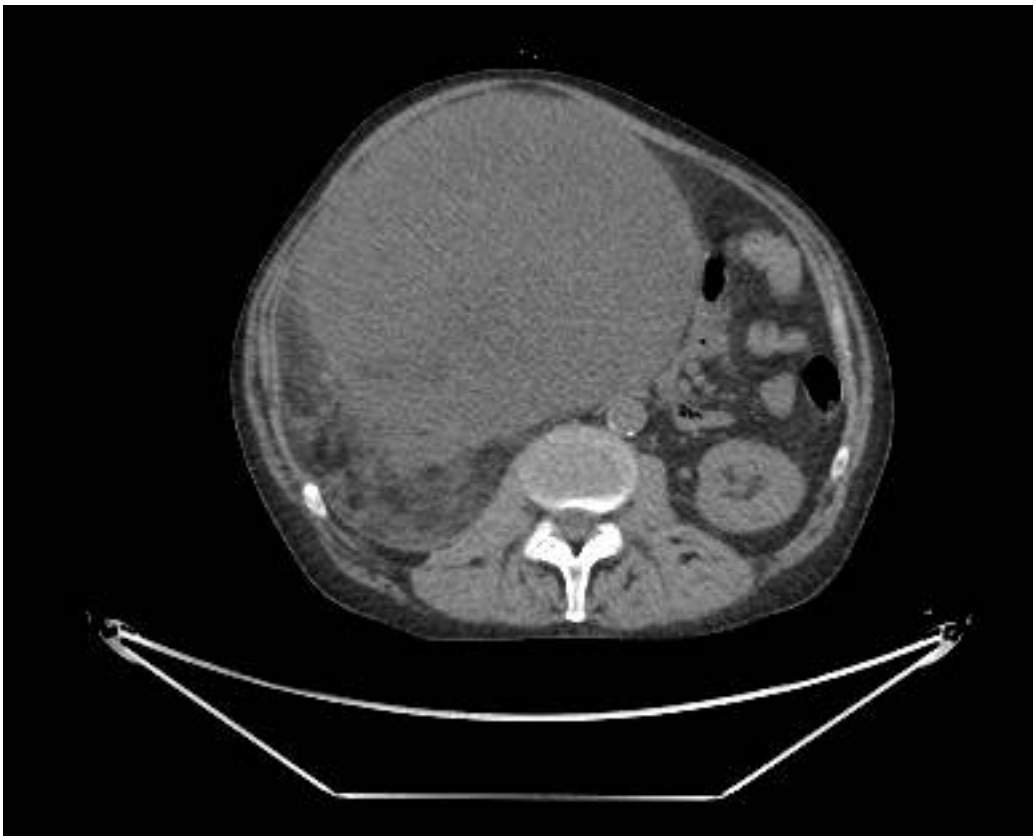
benign tumour	0	3	0	0	0	1	0	0	4 (67%)	0	8
non-diagnostic	0	0	1	0	1	0	1	0	0	0	3
Total	26	43	16	2	5	10	7	1	6	1	117

Table 4: Sensitivity, specificity, PPV and NPV by histological subtype

Histology on biopsy (n=total on biopsy)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Liposarcoma combined (n=61)	0.81 (0.70 to 0.90)	0.90 (0.77 to 0.97)	0.92 (0.82 to 0.97)	0.90 (0.77 to 0.97)
WDLPS (n=38)	0.85 (0.65 to 0.96)	0.82 (0.73 to 0.90)	0.58 (0.41 to 0.74)	0.95 (0.88 to 0.99)
DDLPS (n=23)	0.40 (0.25 to 0.56)	0.92 (0.83 to 0.97)	0.74 (0.52 to 0.90)	0.72 (0.61 to 0.81)
LMS (n=13)	0.81 (0.54 to 0.96)	1.00 (0.97 to 1.00)	1.00 (0.75 to 1.00)	0.97 (0.93 to 0.99)
Myxoid LPS (n=4)	1.00 (0.16 to 1.00)	0.98 (0.94 to 1.00)	0.50 (0.07 to 0.93)	1.00 (0.97 to 1.00)
UPS (n=9)	0.40 (0.05 to 0.85)	0.94 (0.88 to 0.97)	0.22 (0.03 to 0.60)	0.97 (0.92 to 0.99)
SFT (n=8)	0.70 (0.35 to 0.93)	0.99 (0.95 to 1.00)	0.88 (0.47 to 1.00)	0.97 (0.92 to 0.99)
Other sarcoma (n=9)	0.57 (0.18 to 0.90)	0.95 (0.90 to 0.99)	0.44 (0.14 to 0.79)	0.97 (0.92 to 0.99)
Benign tumour (n=8)	0.67 (0.22 to 0.96)	0.96 (0.91 to 0.99)	0.50 (0.16 to 0.84)	0.98 (0.94 to 1.00)

Table 5: Sensitivity, specificity, PPV and NPV according to adjunct pre-biopsy diagnostic testing

Diagnosis on final histopathology and adjunct test (n=total biopsy)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
WDLPS (n=38)	0.85 (0.65 to 0.96)	0.82 (0.73 to 0.90)	0.58 (0.41 to 0.74)	0.95 (0.88 to 0.99)
PET (n=22)	1.00 (0.75 to 1.00)	0.76 (0.59 to 0.88)	0.59 (0.36 to 0.79)	1.00 (0.88 to 1.00)
FISH (n=27)	0.80 (0.56 to 0.94)	0.81 (0.69 to 0.90)	0.59 (0.39 to 0.78)	0.92 (0.81 to 0.98)
PET + FISH (n=16)	1.00 (0.66 to 1.00)	0.71 (0.49 to 0.87)	0.56 (0.30 to 0.80)	1.00 (0.80 to 1.00)
DDLPS (n=23)	0.40 (0.25 to 0.56)	0.92 (0.83 to 0.97)	0.74 (0.52 to 0.90)	0.72 (0.61 to 0.81)
PET (n=11)	0.50 (0.28 to 0.72)	1.00 (0.88 to 1.00)	1.00 (0.72 to 1.00)	0.72 (0.55 to 0.85)
FISH (n=20)	0.56 (0.35 to 0.76)	0.89 (0.77 to 0.96)	0.70 (0.46 to 0.88)	0.81 (0.69 to 0.90)
PET + FISH (n=9)	0.60 (0.32 to 0.84)	1.00 (0.81 to 1.00)	1.00 (0.66 to 1.00)	0.75 (0.53 to 0.90)
LPS (n=61)	0.81 (0.70 to 0.90)	0.90 (0.77 to 0.97)	0.92 (0.82 to 0.97)	0.90 (0.77 to 0.97)
PET (n=33)	0.91 (0.77 to 0.98)	0.93 (0.68 to 1.00)	0.97 (0.84 to 1.00)	0.82 (0.57 to 0.96)
FISH (n=47)	0.94 (0.82 to 0.99)	0.90 (0.74 to 0.98)	0.94 (0.82 to 0.99)	0.90 (0.74 to 0.98)
PET + FISH (n=25)	1.00 (0.86 to 1.00)	0.89 (0.52 to 1.00)	0.96 (0.80 to 1.00)	1.00 (0.63 to 1.00)



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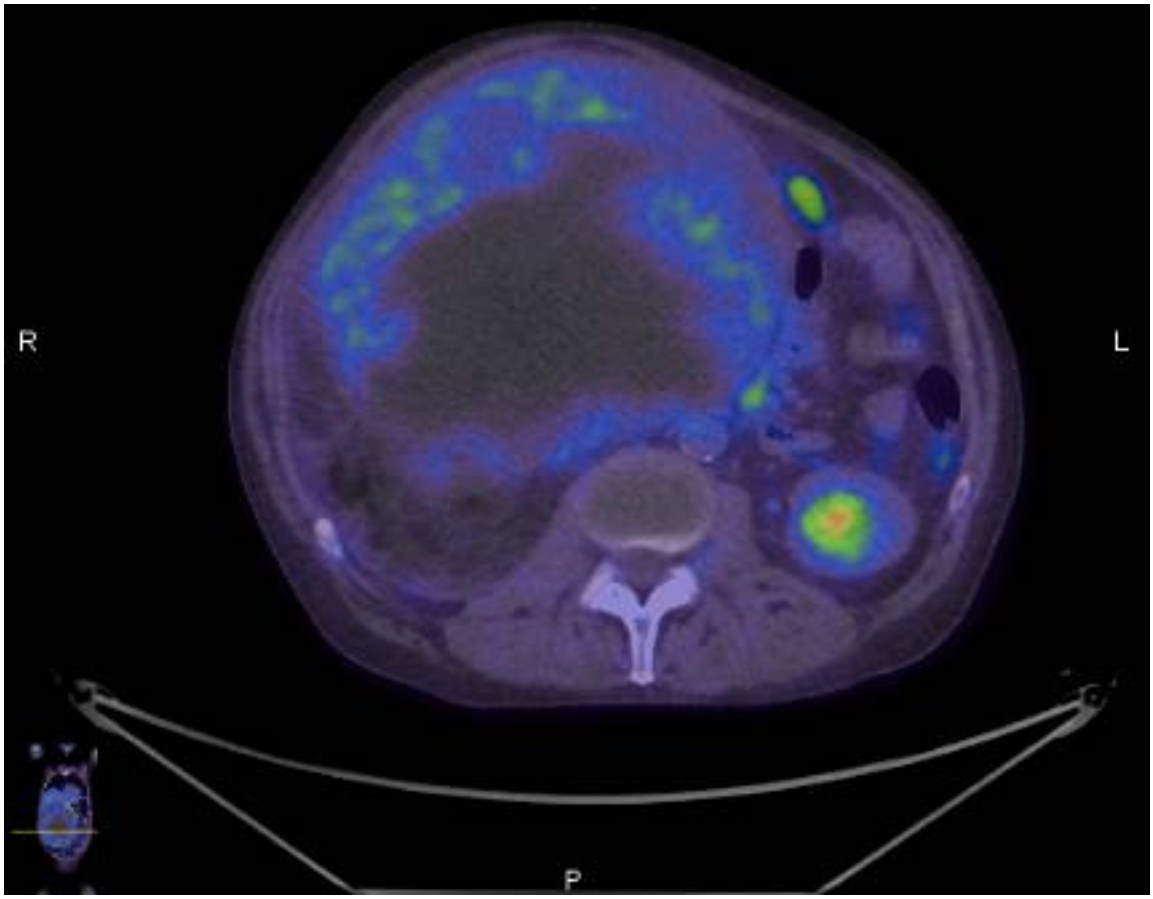
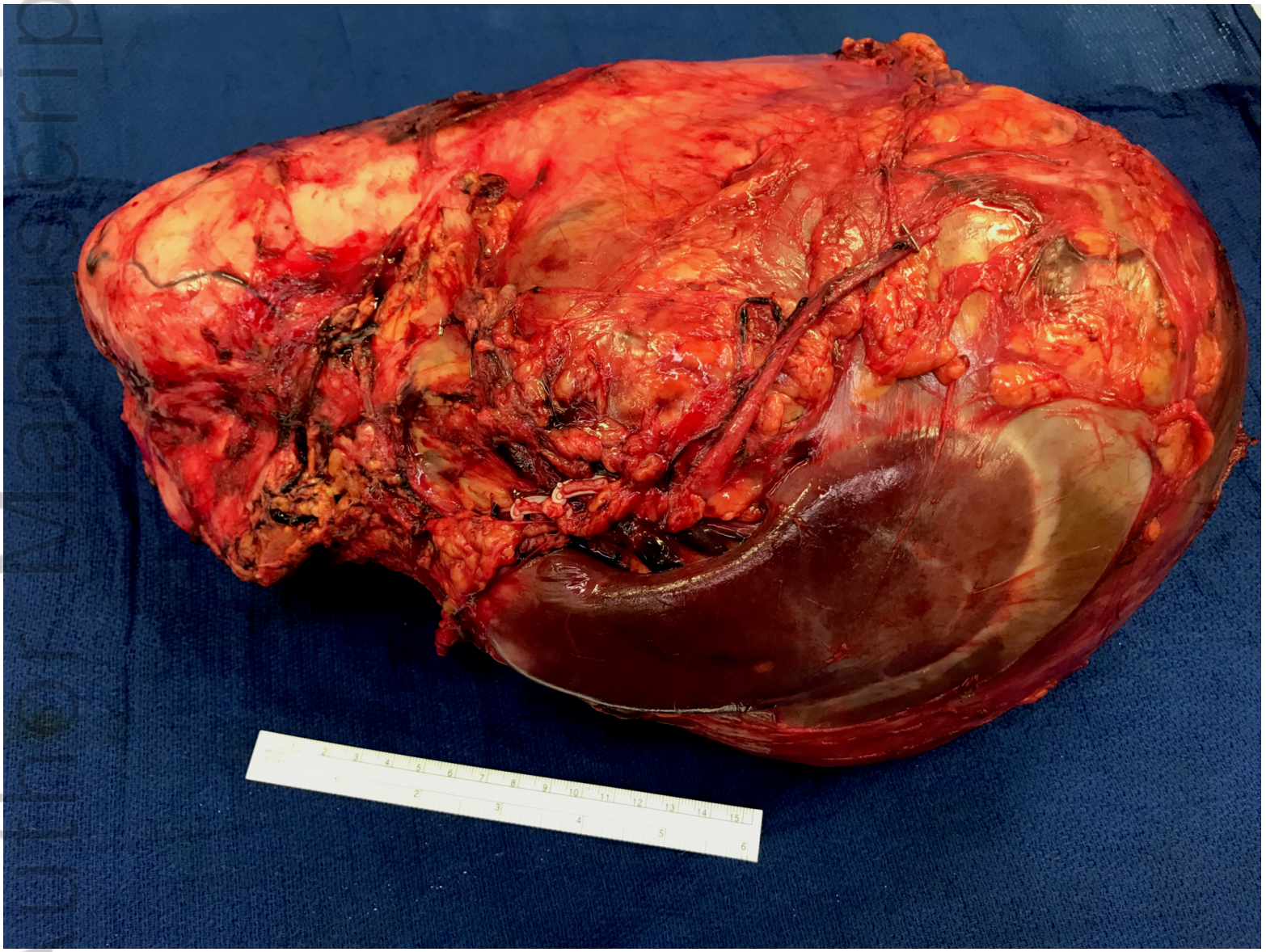


ANS_15723_YoungFig1b.tiff



ANS_15723_YoungFig1c.tiff