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ORIGINAL ARTICLE – SARCOMA

Early and Late Complications of Percutaneous Core Needle Biopsy of Retroperitoneal Tumors at Two Tertiary Sarcoma Centers

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ABSTRACT

Background. Concern persists regarding percutaneous core needle biopsy (CNB) of a potentially malignant lesion of the retroperitoneum due to the perceived risk of immediate complications and adverse oncologic outcomes, including needle tract seeding (NTS).

Objective. The aim of this study was to evaluate the incidence of (1) early complications and (2) NTS following CNB of suspected retroperitoneal sarcoma (RPS).

Methods. Patients who underwent CNB of an RP mass with pre-biopsy suspicion of sarcoma were identified from a prospective database at two centers: (1) Princess Margaret Cancer Centre/Mount Sinai Hospital, Toronto (2009–2015); and (2) The Ottawa Hospital (1999–2015). Early complications, including bleeding, pain, infection, and organ injury, were recorded. Instances of NTS were identified from long-term follow-up of patients who underwent resection of primary RPS at these two centers after initial CNB (1996–2013).

Results. Of 358 percutaneous CNBs of suspected RPS performed over the study period, 7 (2.0%) resulted in minor bleeding with no transfusion, 3 (0.8%) resulted in significant pain, 1 (0.3%) resulted in unplanned admission to hospital for observation, and 1 (0.3%) resulted in a pneumothorax. There were no infections. In 203 patients who underwent resection of RPS following CNB, crude cumulative local recurrence was 24% at 5 years. At a median follow-up of 44 months, there was one case of NTS (approximately 0.5%).

Conclusion. This large bi-institutional experience with CNB of an RP mass demonstrates that both the early complication rate and the incidence of NTS are very low. Physicians and patients can be reassured that the benefits of CNB in diagnosing sarcoma and determining its histologic subtype and grade far outweigh the risks.

Percutaneous core needle biopsy (CNB) of suspected retroperitoneal sarcoma (RPS) is a standard component of pretreatment investigation in specialized sarcoma centers, recommended by consensus guidelines.[1,2] Despite this,

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many patients and referring physicians express concern about potential complications, in particular tumor seeding. This can lead to reluctance and anxiety on the part of the patient, and sometimes refusal of the recommended biopsy, potentially compromising treatment decisions.

In a patient who presents with a newly identified retroperitoneal mass, the benefits of making a histologic diagnosis prior to planning treatment are clear. Benign entities such as benign peripheral nerve sheath tumor (BPNST) and angiomyolipoma can masquerade as RPS, but would not be managed by the same algorithm.[3] Certain malignant entities, such as lymphoma and metastatic germ cell tumor, may be most appropriately managed with upfront systemic therapy.

Biopsy by fine-needle aspiration may sometimes be sufficient to diagnose the broad category of malignancy, such as metastatic adenocarcinoma, but results are frequently nonspecific and unreliable. CNB is highly preferred because it provides tissue architecture for pathologic evaluation. This more reliably identifies histologic subtype and grade, features that guide the choice and sequencing of modern multimodality therapy for mesenchymal tumors. In a series of 371 biopsies of a soft tissue mass that subsequently underwent resection, CNB discriminated sarcoma from benign entities in 98% of cases, high-grade from low-grade lesions in 86% of cases, and provided accurate tumor subtype in 86% of cases.[4]

That said, the complications of CNB of a suspicious retroperitoneal mass have not been systematically documented. Potential early complications include bleeding, pain, infection, and injury to adjacent structures. Furthermore, it has been hypothesized that CNB could be associated with late complications, chiefly compromised oncologic outcomes. The purported mechanism would be through disruption of the tumor pseudocapsule and dissemination of malignant cells. Concern regarding this possibility has been engendered by a disease-specific survival nomogram for liposarcoma (extremity, truncal and retroperitoneal) published in 2006.[5] Pretreatment biopsy was included as a negative prognostic indicator, although it was not clear what type of biopsy was involved. Nomograms developed by groups in Milan and MD Anderson Cancer Center that specifically interrogate overall survival (OS) in RPS do not include pretreatment biopsy as one of the variables of interest.[6,7] It is thus not clear whether pretreatment CNB has any association with compromised outcomes.

Concern focuses on the potential for needle tract seeding (NTS), which requires not only that tumor cells be deposited along the needle tract but also that they proliferate in that environment. The literature on NTS in sarcoma consists largely of case reports, such as exist for many types of solid tumors, including adenocarcinoma arising from almost every primary site,[8–11] melanoma,[12] and sarcoma.[13] The risk of NTS appears histology-specific, with a higher risk reported for hepatocellular carcinoma (2.7%),[14] and much lower estimated risks for thyroid and prostate ($\ll$ 1%).[9,15] For sarcoma, the incidence of NTS is particularly obscure.

The objective of the present study was to describe the early and late complications of CNB in patients referred for management of a retroperitoneal tumor with a suspected diagnosis of sarcoma.

METHODS

To determine the incidence of early, procedure-related complications, consecutive patients who underwent CNB for a retroperitoneal mass were identified in a prospective database at two tertiary centers—Princess Margaret Cancer Centre/Mount Sinai Hospital (PMCC/MSH), Toronto, and The Ottawa Hospital (TOH), Ottawa. For biopsies at PMCC/MSH, prospective follow-up data were available for those completed between January 2009 and December 2015, and between January 1999 and December 2015 for biopsies completed at TOH. Only patients referred to the sarcoma program were included. A final diagnosis of sarcoma was not required for inclusion. Both centers have a clinical research team who track CNB requests and outcomes.

A retrospective chart review was conducted to capture details of any post-biopsy blood transfusion, prescription for analgesics or antibiotics, inpatient admission, and unscheduled return visits to the emergency department or ambulatory clinic. Electronic records of medical imaging encounters were reviewed to identify any immediate complications at the time of CNB, or during 4–6 h spent in the recovery bay. New symptoms that arose within 2 weeks of CNB were considered procedure-related. The Clavien–Dindo system was used to classify complications.[16] Repeat biopsy was considered a new event.

To investigate the incidence of NTS, consecutive patients who underwent CNB before resection of a primary, nonmetastatic RPS between 1996 and 2013 were identified. At both centers, pretreatment CNB was part of the routine investigation of retroperitoneal solid masses over this period. Patients were followed at prescribed intervals (every 4–6 months for 5 years after resection, then annually) with visits that included history and physical examination, and cross-sectional imaging. Tumor recurrence was typically identified by imaging, and was considered confirmed if the mass was new and had radiographic features of a recurrence after review by a dedicated sarcoma radiologist, grew on serial imaging, and/or was biopsy-confirmed. Patients with recurrent disease were

reviewed at multidisciplinary conference, and site(s) of recurrence recorded in the RPS database. To discover any cases of potential NTS in addition to those previously recorded as such,[17] all cases of local recurrence (LR; i.e. intra-abdominal nonhepatic parenchymal) were reviewed in detail to determine whether the site of recurrence could be compatible with NTS, given the needle trajectory used for CNB.

Proportions were compared using the Chi square test, and statistical significance was set at $p < 0.05$. This study was approved by the Research Ethics Boards of MSH and PMCC, Toronto, and TOH Research Institute, Ottawa.

RESULTS

Early Complications

Between January 1999 and December 2015, 314 patients referred with a retroperitoneal mass suspicious for sarcoma underwent a total of 358 CNBs. There were 253 biopsies on 220 patients from PMCC/MSH, and 105 biopsies on 94 patients from TOH.

The pathologic diagnosis made on the basis of the biopsy was sarcoma in 194 of 358 biopsies (54%). In 74 cases (21%), a specific benign diagnosis was rendered (Table 1); in 55 cases (15%), a malignancy other than sarcoma; and 35 cases (10%) were nondiagnostic despite review by additional expert soft tissue pathologists.

In 358 CNB procedures, there were no early complications of grade 2 or higher (Table 2). There was one unplanned admission to hospital for shortness of breath that then resolved spontaneously, with no changes on chest X-ray or electrocardiogram; the patient, who had baseline chronic respiratory dysfunction, was observed for 24 h. The most common early complication of CNB was minor intratumoral bleeding ($n = 7$, 2.0%), which, in all cases, resolved spontaneously without any procedural intervention, and without transfusion. Following three CNBs (0.8%), the patient reported a significant increase in pain that required analgesics. Following one CNB (0.3%), a subclinical pneumothorax was noted; the patient was observed for 4 h, then discharged without intervention. No procedure-related infections occurred. After one procedure, the patient reported both pain and a minor bleed. Overall, 12 grade 1 or 2 complications were documented, for a total early complication rate of 3.4%. There was a higher rate of complications in patients in whom the biopsy was read as benign or nondiagnostic (7/109, 6%) compared with patients with malignant histologies (4/249, 2%; $p = 0.02$). Repeat biopsy was associated with an early complication rate of 6.3% (3/48), compared with 2.9% (9/310) for first-time CNB.

TABLE 1 Pathologic diagnoses made on percutaneous core needle biopsy of retroperitoneal mass (1999–2015)

Diagnosis on biopsy	*N* (%)
Sarcoma	194 (54)
Liposarcoma	107
Dedifferentiated	56
Well-differentiated	22
NOS	29
Leiomyosarcoma	39
Undifferentiated pleomorphic sarcoma	13
Other	35
Other malignancy	55 (15)
GIST	18
Carcinoma	10
Lymphoma; malignant lymphoid tissue	12
Chordoma	2
Paraganglioma	5
Other	8
Other soft tissue neoplasm	74 (21)
Lipomatous lesion	25
Spindle cell neoplasm NOS	17
BPNST (schwanomma)	13
Smooth muscle neoplasm	6
Fibrous tissue	2
Extramedullary hematopoiesis	1
Myxoid neoplasm NOS	1
Angiomyolipoma	1
Other	8
Nondiagnostic	35 (10)
Total	358

GIST gastrointestinal stromal tumor, *BPNST* benign peripheral nerve sheath tumor, *NOS* not otherwise specified

Late Complications

Between January 1996 and December 2013, 203 consecutive patients underwent CNB prior to resection of a primary RPS (166 at MSH, 37 at TOH) (Table 3). The majority of patients (74%) received preoperative external beam radiation, while 22% received no adjuvant therapy pre- or postoperatively. A small proportion (4%) received some other adjuvant regimen (e.g. postoperative brachytherapy).

Median follow-up time post-resection was 44 months (range 1–230, interquartile range 24–72): 114 patients were alive with no evidence of sarcoma, 31 were alive with recurrent sarcoma, 45 were dead of sarcoma, and 13 were dead of other causes. Sixty-nine patients (34%) had developed tumor recurrence by the time of last follow-up (local only, $n = 43$; distant only, $n = 22$; both distant and

TABLE 2 Early complications after percutaneous CNB of a retroperitoneal mass (1999–2015)

	Total [*N* (%)] 358	Malignant [*N* (%)] 249	Benign/nondiagnostic [*N* (%)] 109
Patients with complications after CNB, total	11 (3.1)	4 (2)	7 (6)[b]
Bleed, minor[a]	7[c] (2.0)	3	4[c]
Bleed, major	0	0	0
Pain requiring analgesics	3[c] (0.8)	0	3[c]
Unplanned hospital admission, respiratory distress	1 (0.3)	1	0
Pneumothorax, asymptomatic	1 (0.3)	0	1
Infection	0	0	0

CNB core needle biopsy

[a]Requiring no intervention

[b]$p = 0.02$ versus malignant diagnoses, Chi square

[c]One patient with what proved to be a benign mass had both pain and minor bleeding

TABLE 3 Patterns and rates of recurrence following primary RPS resection after percutaneous CNB (1996–2013)

Type of recurrence	*N* (%)	No adjuvant Rx (pre- or postoperatively) [*N* (%)]	Preoperative XRT (± chemotherapy, ± brachytherapy) [*N* (%)]	Postoperative XRT or perioperative chemotherapy; no preoperative XRT (%)
None	134 (66)	30 (68)	101 (67)	3
Any	69 (34)	14 (32)	50 (33)	5
Local	47[a] (23)	12 (27)	31 (21)	4
Distant	26[a] (13)	3 (7)	21 (14)	2
Needle tract seeding	1 (0.5)	0	1 (1)	0
Total	203	44 (22)	151 (74)	8 (4)

RPS retroperitoneal sarcoma, *CNB* core needle biopsy, *Rx* therapy, *XRT* radiation therapy

Median follow up = 44 months (range 1–230; IQR 24–72)

[a]Four patients had both local and distant relapse

local, $n = 4$). Five-year crude cumulative local and distant recurrence rates were 24% and 13%, respectively.

On review of imaging studies performed at the time of initial detection of an LR and over time thereafter, together with review of CNB procedural descriptions, there was one case in which the site of recurrence was compatible with NTS as the potential etiology (1/47 LRs; 1/203 patients who had CNB plus resection, 0.5%). This patient originally presented with a mass that invaded the abdominal wall and flank muscles, as well as paravertebral muscles at the transverse processes of T10 and T12, intercalating between the posterior aspect of the ribs. CNB from a posterior approach yielded a diagnosis of 'high-grade malignant fibrous histiocytoma' in 2004. The tumor was initially deemed unresectable and was treated with external beam radiotherapy (24 Gy over 2 weeks), but expanded. The patient then received two cycles of single-agent doxorubicin, with an eventual decrease in the size of the mass; en bloc resection was then performed. Nine months later, computed tomography showed three clustered nodules, each measuring 1–2 cm, on the posterior fascial surface of the paraspinal muscles. CNB confirmed recurrent disease, with histologic appearance matching that of the primary tumor. The recurrent tumor was excised via a posterior approach. The location was consistent with NTS, although microscopic extension beyond the margin of primary resection could not be ruled out as an underlying mechanism.

DISCUSSION

Cancer recurrence reflects a complex interplay of tumor, patient, and treatment factors, including physico-mechanical forces. The possible role of iatrogenic tumor cell seeding in the pathogenesis of cancer recurrence is challenging to dissect. In the example of incidentally discovered gallbladder adenocarcinoma following laparoscopic cholecystectomy for what was thought to be benign

biliary pathology, the development of port-site metastases might be the direct result of seeding and engraftment at the port sites. When this pattern of recurrence was first recognized in the 1990s,[18–20] there was considerable debate as to whether it was safe to proceed with laparoscopic resection for any type of cancer because of the potential for recurrence within port-site wounds. However, with more rigorous study, it became apparent that the risk of port-site recurrence was not appreciably different than that of laparotomy wound recurrence after open resection of colorectal adenocarcinoma, or gastric adenocarcinoma.[21,22] The debate regarding the safety of minimally invasive surgery for oncologic resections has been reignited, with a recent trial demonstrating worse disease-free survival and OS in women undergoing minimally invasive radical hysterectomy compared with open hysterectomy for early-stage cervical cancer.[23] The spectre of disruption of a malignant tumor, whether through operative transgression or percutaneous needle biopsy, can make both clinicians and patients wary. As with any investigational or therapeutic procedure, the benefits and risks of CNB in the work-up of a suspicious retroperitoneal mass need to be carefully weighed and the potential risks minimized.

In the work-up of potential soft tissue sarcoma, whether of the extremity or retroperitoneum, pretreatment confirmation of the diagnosis, including specific histologic subtype and grade, is standard; the appropriate treatment regimen and sequencing can vary widely depending on these features. For extremity sarcoma, consensus guidelines stipulate that pretreatment biopsy should be performed in such a way that the biopsy tract/site will be included in the resected specimen. In studies that examine the histology of resected needle tracts in extremity sarcoma, 13% of these harbored malignant cells.[17,24–27] However, in studies that followed patients who did not have the biopsy needle tract excised at the time of wide local excision (n = 30), no patients developed NTS.[28,29] There could be many underlying factors, including insufficient tumor cell inoculum to induce angiogenesis and evade host defenses, and the sterilizing effect of adjuvant treatments.

In the case of RPS, the needle biopsy route is chosen to minimize the risk to intra-abdominal viscera and to critical retroperitoneal structures such as the aorta, inferior vena cava, and renal hilum, and is limited by bony structures, including the vertebra, sacrum, and iliac crest. The tract is not usually planned with a view to eventual en bloc resection with the specimen, and the latter is not typically performed or attempted. In the past, some clinicians expressed concern about the potential for NTS associated with this scenario, instead advising upfront resection of technically resectable masses.[30] However, the disadvantages of major resection for asymptomatic benign entities, or histologies best treated with induction systemic therapy, are readily apparent. Biopsy should not be omitted, as even expert radiologists at a tertiary referral sarcoma center have been unable to reliably anticipate specific histologic subtypes of retroperitoneal soft tissue masses based on imaging alone.[31] In the present series, 21% of biopsies of a suspected RPS proved to have a specific benign diagnosis on CNB, and 10% of biopsies did not render any specific diagnosis. Moreover, for 15% of biopsies, a malignancy other than RPS was diagnosed. In all these settings (totaling 46% of biopsies performed), the decision for, choice of, and sequencing of therapies were different to what would have been done were the mass assumed to be RPS.

In our experience, the risk of early complications following CNB of a suspicious RP mass was low (< 4% of procedures), and the few complications that did occur were of a mild and self-limited nature, and none impacted further therapy. The minor complication rate was slightly higher in the cohort of patients who proved to have a benign diagnosis, or for whom a diagnosis could not be reached, possibly related to the propensity for CNB of schwannoma to cause transient pain. Overall, our results are concordant with those reported by Wilkinson et al., in which only one early complication, a rectus sheath hematoma, was documented in a series of 90 patients.[32]

Based on the present series, the risk of NTS following CNB of primary RPS appears to be on the order of 0.5%. For RPS, LR is defined as that occurring anywhere within the abdominal cavity, including the retroperitoneum itself, but outside of the hepatic parenchyma. To better assess the long-term oncologic risks of CNB, one would ideally compare recurrence rates and OS in cohorts of RPS patients who did and did not undergo pre-resection biopsy. This is challenging, given the lack of prospectively collected data and many other differences in management at recognized centers of excellence, as well as the differences in outcome based on specific histology and grade of RPS.[33,34] Beyond these restrictions, there is the salient limitation that in high-volume centers, there are currently very few patients who do not undergo pretreatment CNB.

We emphasize the advances made in CNB technique, in particular the importance of a co-axial approach using a sheathed needle.[22] In 255 patients who underwent biopsy before resection of RPS at the Royal Marsden or Netherlands Cancer Institute (1990–2014), Van Houdt et al.[35] reported biopsy site recurrence in five (2%). Interestingly, all five occurred following transabdominal biopsies performed without the co-axial technique. Such technical factors could explain the higher incidence in their series. A review of the literature on NTS in RPS showed that only three other cases have been reported to date, in an overall experience of thousands of biopsies.[13,32,36,37]

We acknowledge the limitations inherent in any retrospective review, albeit of cases collected in a prospective manner. Ascertainment bias could have led to underestimation of the risk of early complications; some adverse events, particularly minor ones, may not have been documented. The incidence of postprocedural pain may not have been accurately captured, given that this would be variably reported and documented at subsequent follow-up visits. However, we are confident that no complication that required a procedural intervention occurred, as this would be reliably captured in the patient record. We emphasize that all patients who are referred with an RP mass are entered into a prospective database, and followed.

It is possible that we have underestimated the true risk of NTS. Because we maintain comprehensive long-term follow-up of patients with serial surveillance imaging at prescribed intervals, patients who develop recurrence following resection of primary RPS are reliably identified, typically prior to any symptoms. While it was possible to infer the relationship of the site of recurrence to the location of the percutaneous needle tract, some instances of intraperitoneal recurrence could theoretically have represented NTS, even though they appeared remote from the tract.

The minimal procedural and oncologic risks we demonstrate here support the routine use of CNB in the work-up of a retroperitoneal mass, as recommended by consensus.[2] Biopsy results should be reviewed in the context of a Multidisciplinary Conference with concomitant review of imaging. In the case of soft tissue sarcoma of the retroperitoneum, histologic subtype and grade will guide the decision making regarding preoperative therapy, and will inform the operative plan. Biopsies are paramount in establishing an appropriate, individualized treatment course. Our findings indicate that the risk of NTS is very low and that there is no reason to omit CNB on such grounds.[2] Investigation and management of a suspicious retroperitoneal mass should be undertaken by a specialized team with expertise in the treatment of RPS and related entities.

CONCLUSION

Percutaneous CNB performed as part of the investigation of suspected RPS was associated with very low early and late complication rates (3.1% and 0.5%, respectively). Early complications were minor and self-limited. In the work-up of a retroperitoneal mass, pre-biopsy review of cross-sectional imaging by a multidisciplinary team, and use of a co-axial sheathed biopsy needle, are important to maximize the benefit–risk ratio of CNB.

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