Topic 2: Retroperitoneal Sarcoma

Question 3: What is the role of preoperative biopsy in retroperitoneal sarcoma? Safety, accuracy?

- **P**opulation: Adult patients with retroperitoneal sarcomas
- **I**ntervention: Preoperative biopsy
- **C**omparator: no biopsy
- **O**utcomes: biopsy tract seeding, recurrence free survival, overall survival

Retroperitoneal sarcomas (RPS) represent a rare and heterogenous group of tumours. Three main histological subtypes account for over 80% of retroperitoneal sarcomas (well-differentiated liposarcoma, de-differentiated liposarcoma, leiomyosarcoma), and the subtypes have significant variation in biological behaviour and outcomes. Local recurrence is more frequent for well-differentiated LPS, whereas other subtypes such as leiomyosarcoma and de-differentiated liposarcoma have a higher risk of developing distant metastases after local resection.

The role of preoperative biopsy is to obtain a histological diagnosis and enable appropriate multidisciplinary treatment planning including enrolment into a clinical trial. However, concern still exists regarding potential complications associated with biopsy including biopsy tract seeding and impact on local recurrence and survival. Previous research has indicated that a coaxial technique with a sheathed needle is the safest method, and that biopsy should be performed under image guidance.

Clinical studies evaluating the safety of preoperative biopsy in retroperitoneal sarcoma rarely compared local recurrence and overall survival for patients who had undergone biopsy to those that had not. Available evidence for this question comes from a limited number of retrospective studies with small sample size.

Systematic literature review only identified 5 studies for this clinical question (1-5). Core biopsy was not routinely conducted with the minority of patients receiving core needle biopsy across all studies (45.6% of total patient population n=3834). Only two included studies (4, 5) described the core biopsy technique. No study specifically compared complications or survival outcomes following biopsy through specialist centre versus other institutions.

Heterogeneity exists in the five publications with respect to the classification, grouping and grading of the different histological subtypes of retroperitoneal sarcoma. There was also variation in which retroperitoneal tumours were biopsied, with the majority of studies reporting that centres do not routinely perform preoperative biopsy of resectable RPS if imaging is judged diagnostic of a well-differentiated or de-differentiated liposarcoma (3-5). Due to the retrospective nature of the studies, it is impossible to determine the reason why biopsy was or was not carried out in each individual case.

It should be noted that the patient source for two of the studies (4, 5) was the Royal Marsden NHS Foundation Trust database. Both studies included patients from the database who underwent resection of primary retroperitoneal sarcoma during a similar time period; Van Houdt et al. between 1990-2014, and Wilkinson et al. between 1990-2011. There is therefore some overlap in the patients included in the studies but the exact number is unable to be determined.

Biopsy Tract Seeding

There are three studies reporting on biopsy tract seeding (1,4-5). All are retrospective cohort studies from UK, Netherlands and Japan. Two studies found no recurrence along biopsy route (1, 5). The number of patients in these studies were 422 and 150. In the larger study by Van Houdt et al., 498 patients underwent resection of primary retroperitoneal sarcoma in the UK and Netherlands (Royal Marsden NHS foundation Trust Database and The Netherlands Cancer Institute) (4). 51.2% of these patients had a preoperative biopsy and 2% (n = 5) developed biopsy site recurrence. The histological subtypes were grade 2 leiomyosarcoma (n=3) and dedifferentiated liposarcoma (n=2). These patients were biopsied trans-abdominally, with multiple passes and not with co-axial technique. Three patients had at least two biopsy attempts as the initial biopsy outside of the institution was non-diagnostic. None of the patients received (neo) adjuvant chemotherapy or radiotherapy and two patients presented with distant metastases around the same time as biopsy tract recurrence. There was increased risk of biopsy tract recurrence when non co-axial method used (p=0.02) but no significant difference in occurrence of biopsy tract recurrence for route of biopsy (p=0.11), noting low number of events. It should be noted that the study had a short median follow up of 38 months, and biopsy tract recurrence occurred between 6 months and 7 years post biopsy.

Local recurrence

There are three studies reporting on local recurrence (2, 4-5). All are retrospective studies from Australia, UK and Netherlands and the number of patients range from 138 to 498.

The one Australian study included, authored by Snow et al. (Peter MacCallum Cancer Centre), studied the management and outcomes of patients undergoing surgery for primary, non-metastatic retroperitoneal sarcoma at an Australian specialist sarcoma centre compared to non-specialist centres (2). They defined local recurrence as recurrence occurring within the retroperitoneum or peritoneal cavity, and in cases of macroscopically incomplete resection, local recurrence was considered to have occurred if there was radiological progression of the residual tumour. They did not specify if liver metastases were included as local recurrence. They found that not employing a biopsy was associated with higher 5-year local recurrence, with HR 2.8 (95% CI 1.1-7.0, p=0.019). It should be noted that patients at the specialist centre had a significantly higher rate of preoperative biopsy (92% v 31%, p <0.001). The population of patients at the specialist centre was made up of a higher proportion of patients with well-differentiated liposarcoma and dedifferentiated liposarcoma, lower grade tumours and received significantly higher rates of neoadjuvant radiotherapy (87% vs 12%, p <0.001). Practice at the specialist centre was to limit extended multi-visceral resection to histologic subtypes where local recurrence is likely to be the cause of future morbidity. Multivariate analysis was not carried out to adjust for possible confounding variables and no specific comparison of survival outcomes following biopsy at the specialist centre versus other centres was analysed.

Two studies reported no significant difference in local recurrence between patients who underwent biopsy to those that did not (4-5). In the study by Van Houdt et al., local recurrence was defined as intra-abdominal recurrence and they did not specify if biopsy tract recurrence or liver metastases are included in the definition. The median time to local recurrence was 14 months, with no significant difference in local recurrence rate for biopsy versus no biopsy (p=0.3) (4). Examination of biopsy route found no significant difference in local recurrence between trans-abdominal and trans-retroperitoneal route (p=0.72). In multivariate analysis adjusting for age, gender, tumour size, grade, histological subtype, use of (neo) adjuvant radiotherapy and chemotherapy, and co-axial needle biopsy, the biopsy route did not significantly correlate with local recurrence rate.

Wilkinson performed analysis of 127 patients from the UK Royal Marsden NHS Foundation Trust database who had tumour resection with complete macroscopic clearance (5). Local recurrence was defined as intra-abdominal, non-hepatic recurrence. No significant difference in local recurrence free survival was found in patients undergoing preoperative biopsy versus no biopsy in either the total population (HR 1.19, 95% CI 0.73-1.94, p=0.132) or in a subgroup of patients classified as liposarcoma (n=96) (HR 1.29, 95% CI 0.71-2.26, p=0.107). The histological subtypes included under the classification of liposarcoma are not described and hence may include several subtypes with very different behaviours, and the study only included intermediate and high grade retroperitoneal sarcomas (unlikely to include well-differentiated liposarcoma). Multivariate analysis showed the only significant factors between the biopsy and no biopsy groups for local recurrence free survival were increase in tumour grade and negative resection margins.

Overall survival

Three studies reported the 5-year overall survival (2-3, 5). The largest study by Straker et al. retrospectively analysed data from the United States National Cancer Database of 2620 patients with non-metastatic RPS who underwent tumour resection between 2006-2014 (3). 1110 of the 2620 patients underwent preoperative biopsy. Those who underwent biopsy had significantly worse 5-year overall survival (57.8% biopsy vs 62.6% no biopsy, p = 0.003), however this survival difference was not seen when a subgroup of patients underwent propensity matching to account for the significant difference in baseline characteristics. In the unmatched cohort, patients with smaller tumours, those treated at high volumes centres and those with non well-differentiated LPS histology were significantly more likely to undergo preoperative biopsy. Multivariate analysis adjusted by age, sex, race, tumour size, grade, clinical stage, histology, preoperative radiation therapy, preoperative systemic therapy, radical resection, tumour resection and facility type, found no impact on overall survival by undergoing preoperative biopsy (HR 1.14, 95%CI 0.98-1.32, p=0.07). In the multivariate analysis, preoperative radiation therapy, preoperative systemic therapy, radical surgical resection and complete resection were all significantly associated with having undergone preoperative biopsy.

Wilkinson et al found no difference in overall survival when comparing 150 patients with retroperitoneal sarcoma (HR 1.27, 95% CI 0.82-1.95, p = 0.264) (5). Univariate analysis of the subgroup of 96 patients classified as liposarcoma found a significant decrease in overall survival in the biopsy group (HR 1.84,1.21-3.22, p =0.01), however this was not significant on multivariate analysis (HR 1.38, 95% CI 0.85-2.26, p=0.191). Snow et al found no significant difference in 5-year overall survival rates (HR 1.4, 95%CI 0.51- 3.6, p = 0.55) (2).

Evidence summary	Level	References
Evidence suggests preoperative co-axial core biopsy of retroperitoneal sarcoma is safe and biopsy tract recurrence is extremely uncommon	III-2	1,4-5
Preoperative core needle biopsy of retroperitoneal sarcoma does not appear to increase local recurrence	III-2	2, 4-5
Preoperative core needle biopsy of retroperitoneal sarcoma does not appear to affect overall survival	III-2	2-3, 5

Evidence-based recommendation	Grade
Preoperative co-axial core biopsy of suspected retroperitoneal sarcomas is recommended.	B

Practice point
Patients with suspected retroperitoneal sarcoma should be referred to a specialised sarcoma multidisciplinary team for early management including preoperative biopsy. This enables accurate histological and molecular subtyping for multidisciplinary treatment planning.

References

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