THE ASSOCIATION BETWEEN DISTANCE FROM A SARCOMA REFERRAL CENTRE AND ONCOLOGIC OUTCOMES IN PATIENTS UNDERGOING TREATMENT FOR RETROPERITONEAL SARCOMA

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ABSTRACT (ENGLISH)

Introduction: Retroperitoneal sarcomas (RPS) are rare malignancies requiring specialized care in referral centers. In a context where late onset of symptoms is common in patients presenting with RPS and where only select referral centers are capable of managing this disease, do patients who live further away from a sarcoma referral centre have worse oncologic outcomes? Our objective was to conduct a review of patients treated for RPS at our institution to identify whether increased distance from a sarcoma referral centre was a prognostic factor in the management of RPS.

Methods: A retrospective cohort study of patients seen in consultation for RPS at a single tertiary referral center from 2008 to 2019 was performed. Patients were separated into "metropolitan area" (MA) group if they lived within the census metropolitan area of the sarcoma centre and were compared to patients living "outside the metropolitan area" (OMA). The primary outcomes were disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS). DFS, PFS, and OS were analyzed using Kaplan-Meier curves and multiple Cox regression.

Results: A total of 101 patients were included in the study. The average age was 61 years and 50.5% of patients were female. Patient baseline characteristics were comparable between groups. Patients in the OMA group were almost twice as likely to present with metastatic disease (MA:11.8% vs OMA:22.7%, SMD:0.291). In both groups, the most common histologic subtype found for RPS was dedifferentiated liposarcoma in 35.6% of patients. 28% of the cohort received neoadjuvant radiation (SMD: 0.048) and 74% underwent surgical resection (SMD:

0.137), proportions of which were comparable between groups. Patients in the MA group had a higher DFS (MA:35.8 months (SD: 31.7) vs OMA:28 months (SD:25.8), SMD 0.270) but there was no difference between groups in the multivariable Cox regression analysis (p=0.437). Patients in the MA group had a higher PFS (MA:16 months (SD:17.84) vs. OMA:5.9 months (SD:3.0), SMD:0.794). In the multivariable analysis, when adjusting for age and histologic subtype, patients in the OMA group were still found to have a higher risk of disease progression (HR 3.50, 95%CI 1.14-10.75, p=0.029). Patients in the MA group also had a higher OS (MA:44.5 months (SD:39.6) vs OMA:30.2 months (SD:25.5), SMD:0.430). In the multivariable analysis, when adjusting for age and histologic subtype, patients in the OMA group demonstrated a lower overall survival (OMA: HR 2.10, 95%CI 1.05-4.23, p=0.037).

Conclusion: This retrospective cohort studies suggests that patients with RPS who live outside the sarcoma referral centre's census metropolitan area, and therefore further away from the referral centre, have lower PFS and OS. This is the first Canadian study demonstrating a distance decay effect in RPS. Further studies are needed to better understand the mechanisms of increased distance that lead to worse oncologic outcomes.

RÉSUMÉ (FRENCH ABSTRACT)

Introduction: Les sarcomes rétropéritonéaux (SRP) sont des tumeurs malignes rares qui nécessitent une prise en charge spécialisée dans les centres de référence. Avec l'apparition tardive des symptômes chez les patients atteignent de cette maladie qui ne peuvent être traités que dans des centres de référence spécifiques, on se demande si les patients qui vivent plus loin d'un centre de référence pour les SRP ont-ils des résultats oncologiques inférieurs? Le but de cette étude était de procéder à examiner les patients traités pour une SRP dans notre établissement afin d'identifier si l'éloignement d'un centre de référence des sarcomes peut agir comme facteur pronostique dans le traitement des SRP.

Méthode: Une étude de cohorte rétrospective a été réalisée de patients atteints de SRP évalués dans une clinique spécialisée dans un seul centre de référence tertiaire entre les années 2008 et 2019. Les patients ont été divisés en deux groupes: le groupe « région métropolitaine » (RM) pour les patients qui vivaient dans la région métropolitaine du centre des sarcomes. Ces patients ont été comparés aux patients vivants « hors de la région métropolitaine » (HRM). Dans cette étude, le but principal était la survie en période de rémission, la survie sans progression et la survie globale. Ces trois critères ont été analysés à l'aide des courbes de Kaplan-Meier et avec la régression de Cox.

Résultats: 101 patients ont été inclus dans l'étude. L'âge moyen des patients inclus dans l'étude était de 61 ans, avec 50,5 % des patients qui étaient des femmes. Les caractéristiques de référence des patients étaient comparables entre les deux groupes. Les patients du groupe

HRM étaient presque deux fois plus susceptibles de présenter avec une maladie métastatique (RM: 11,8 % vs HRM: 22,7 %, différence moyenne normalisée (DMN): 0,291). Dans les deux groupes, le sous-type histologique le plus courant pour le SRP était le liposarcome dédifférencié dans 35,6% des patients. Vingt-huit % des patients ont reçu de radiothérapie néo-adjuvante (DMN: 0,048) et 74 % ont subi une résection chirurgicale (DMN: 0,137), où les proportions étaient comparables entre les deux groupes. Les patients du groupe RM avaient une survie en période de rémission plus élevée (RM: 35,8 mois (DS: 31,7) vs HRM: 28 mois (DS: 25,8), DMN: 0,270), mais il n'avait aucune différence entre les deux groupes dans l'analyse de régression multivariée de Cox (p = 0,437). Les patients du groupe RM avaient une survie sans progression plus élevée (RM: 16 mois (DS: 17,84) vs HRM: 5,9 mois (DS: 3,0), DMN: 0,794). Dans l'analyse multivariée, après un ajustement pour l'âge du patient et le sous-type histologique, les patients du groupe HRM présentaient toujours un risque plus élevé de progression de la maladie (HR 3,50, IC à 95 % 1,14-10,75, p = 0,029). Les patients du groupe RM avaient également une survie globale plus élevée (RM: 44,5 mois (SD: 39,6) vs HRM: 30,2 mois (SD: 25,5), SMD: 0,430). Dans l'analyse multivariée, lors de l'ajustement pour l'âge du patient et le sous-type histologique, les patients du groupe HRM ont démontré une survie globale inférieure (HRM: HR 2,10, IC à 95 % 1,05-4,23, p = 0,037).

Conclusion: Cette étude de cohorte rétrospective suggère une diminution de la survie sans progression et la survie globale chez les patients atteignent de SRP qui vivent en dehors de la région métropolitaine du centre de référence des sarcomes et donc plus éloignés du centre de

référence. C’est la première étude canadienne démontrant cet effet dans les SRP. D'autres études sont nécessaires pour mieux comprendre les mécanismes de ce phénomène.

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CONTRIBUTION OF AUTHORS

Dr. Giuseppe Frenda wrote this thesis in its entirety. He was also the first author for the manuscript included in the thesis. For the manuscript, he was involved in the study design, data acquisition, data analysis with interpretation of results, and composing of the manuscript.

Dr. Sinziana Dumitra was the thesis co-supervisor. She is the senior author on the manuscript and provided substantial contributions to the study design, acquisition of patient list, data analysis and interpretation of results. She oversaw and provided feedback to both the manuscript and thesis

Prof. Erin Strumpf was the main thesis supervisor. She provided substantial contributions to the study design, data analysis and interpretation of results. She oversaw and provided feedback to both the manuscript and thesis.

Mr. Sukhdeep Jatana is a medical student at McGill University and provided substantial contributions to data acquisition for the patients included in the manuscript.

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CHAPTER 1 – INTRODUCTION

1.1 Epidemiology and general principles of soft tissue sarcomas

Soft tissue sarcomas (STS) are a group of rare tumors which derive from mesenchymal (connective tissue) cells, examples of which include bone, cartilage, fat, and blood vessels. There are over fifty subtypes of sarcomas, which highlights the heterogenous nature and behaviour of this malignancy[1]. Sarcomas account for 0.7% of new cancer cases in the United States with a median age of diagnosis of 61 years old. STS are more common in males and has been increasing over time, from 2.2 cases per 100,000 people in 1975 to 3.5 cases per 100,000 in 2017 in the United States[2]. In Canada, 1,025 Canadians were diagnosed with STS in 2016[3]. The 5-year survival for STS is 65%, however this decreases to 16% for patients with metastatic disease[2] .

Most cases of STS arise sporadically, however certain risk factors have been identified for this disease. Many genetic syndromes have also been associated with sarcomas, examples of which include Werner syndrome, Li-Fraumeni syndrome, and neurofibromatosis type 1[4]. Radiation therapy, used as part of treatment for many malignancies, is a known risk factor for development of sarcoma. On average, sarcomas develop after 10 years from receipt of radiation, and are more common after adjuvant radiotherapy in the context of breast conserving surgery for breast cancer[5].

STS can form anywhere in the body, but most commonly appear in the extremities, chest wall, and retroperitoneum. Sixty percent are found in the extremities, more commonly occurring in the lower limbs, with 20% occurring in retroperitoneal and intraperitoneal sites[6,7]. Anatomic location of disease is an important consideration in symptom presentation. STS can present as painless rapidly growing mass found under the skin or in deeper anatomic spaces.

Extremity sarcomas often present with a lump, which is easily palpable and can be detected by the patient given the superficial location of most soft tissue in the extremity as well as the small compartments. Retroperitoneal sarcomas (RPS), which occur in the retroperitoneal space, can grow to very large sizes (> 30 cm) before causing symptoms which are vague in nature, such as abdominal pain, weight gain, neurovascular, or musculoskeletal symptoms. As such, patients can present with larger tumor sizes in RPS when compared to extremity sarcoma[8].

In general, sarcomas spread by a mechanism of direct local extension into adjacent tissues and structures. Fascia, cartilage, vascular adventitia, periosteum, and mesothelial tissues are less likely to be invaded directly by soft tissue sarcoma. As such, these tissues can be seen as barriers to cancer spread. Lymph node involvement in STS is not common, however in a heterogenous malignancy such as STS, certain exceptions apply, examples of which include clear cell and epithelioid sarcoma[9]. The most common site of metastases in STS remains the lungs[10].

Many treatment modalities exist for STS, however, the only treatment which can be curative is complete en-bloc surgical resection[11]. Other treatment modalities, such as chemo and radiation therapy are commonly used in STS, either as an adjunct to surgery or for palliative treatment in the context of metastatic disease. Important prognostic factors exist for both local and distant recurrence or spread of disease. Local recurrence (LR) is defined as spread from the origin to the surrounding tissue or lymph nodes. Distant recurrence/metastases is defined as spread from the cancer's origin to distant organs or lymph nodes. The term "recurrence" is used once surgical resection is achieved with surveillance imaging or clinical examination demonstrating recurrent disease either locally or to distant organs/lymph nodes.

The most important prognostic factors for local recurrence is completeness of surgical resection[12]. Completeness of surgical resection (also referred to as resection classification) is divided into 3 groups: R0, R1, and R2. R0 resection refers to microscopically negative margins, which means that no gross or microscopic tumor remains in site of origin where the sarcoma was removed. An R1 resection refers to the complete removal of the tumor, however, when the outermost edge of the resected tumor is seen under the microscope, tumor cells are identified. An R2 resection occurs when macroscopic residual tumor that was not resected[13]. In RPS similar results are seen in R0 and R1 disease, however they differ dramatically from R2 disease. Other prognostic factors for local recurrence in STS include tumor size, grade, histologic subtype, and anatomic location. In distant recurrence, the most important prognostic factors are tumor grade, size, and histologic subtype[12].

RPS are sarcomas originating in the retroperitoneal space. They can develop from any of the soft tissues of the retroperitoneum, and have significant histologic overlap with sarcomas seen in the extremity. The most common histologic subtypes in RPS are dedifferentiated liposarcoma (DDL) (37%), well-differentiated liposarcoma (WDL) (26%), leiomyosarcoma (LMS) (19%), Solitary fibrous tumor (6%), malignant peripheral nerve sheath tumor (MPNST) (3%), and undifferentiated pleomorphic sarcoma (UPS) (2%) remain rarer[12].

Liposarcoma is a soft tissue sarcoma which originates from fat cells. They are often characterized by amplification of the MDM2 gene on immunohistochemistry. WDL is a slow growing STS that rarely metastasizes and has a propensity for local recurrence. WDL is the most common malignant adipocytic neoplasm in humans and occurs in both the extremities and the retroperitoneum[14]. WDL can dedifferentiate to DDL (although approximately 90% of cases are

sporadic in DDL), which is more clinically aggressive and has a greater risk of local recurrence and metastatic disease[15].

LMS arises from smooth muscle cells, predominantly from large blood vessels. They are often stained for actin and desmin specific to smooth muscle on immunohistochemistry[16]. They can form in many parts of the body including the uterus, large blood vessels, skin, gastrointestinal tract and retroperitoneal space. Leiomyosarcomas are aggressive lesions which occur predominantly in women and have a greater metastatic potential than liposarcoma[17].

MPNST are soft tissue sarcomas which originate from elements of the nerve sheath. They occur predominantly in men and approximately 25-50% of cases occur in patients with neurofibromatosis type 1. Historically, MPNST has been one of the more difficult soft tissue lesions to diagnose, in part because of a lack of a standardized diagnostic criteria as well as absence of specific biomarkers. MPNSTs are generally high-grade sarcomas in nature, and have a high probability of local and distant metastasis. MPNSTs as a whole are chemoresistant and patients most commonly present to clinic with stage III disease, making it a challenging subtype to treat.

UPS, previously known as malignant fibrous histiocytoma, are a group of unclassified sarcomas with no definable line of differentiation through immunohistochemistry, however, fibroblastic features have been identified on electron microscopy[17]. Some molecular studies have suggested that retroperitoneal UPS are very similar to DDL[18]. Approximately one third of patients develop metastatic disease, with the most common site of metastasis being the lung[17].

1.2 Retroperitoneal Sarcomas

As the name would suggest, RPS occur in the retroperitoneum, an anatomic space located in the posterior aspect of the abdomen, between the posterior abdominal wall and the parietal peritoneum (peritoneum which lines the abdominal and pelvic cavities) (Figure 1.1). Organs in the abdomen that are not suspended by a mesentery (fold of peritoneum containing blood vessels and lymphatics) located between the abdominal wall and parietal peritoneum are located in the retroperitoneum[19]. The retroperitoneum contains organs and vital structures such as the kidneys, adrenal glands, pancreas, aorta and its major branches, the inferior vena cava and its tributaries, the femoral nerve, as well as the ilacus and psoas muscles.

The retroperitoneum is divided into 3 or 4 main anatomic spaces: (1) The anterior pararenal space contains most of the pancreas (head, neck, and body), the ascending and descending colon, and all but the proximal first part of the duodenum. (2) The perirenal space includes mostly organs of the genitourinary system, including the kidneys and ureters, adrenal glands, as well as the renal vein and artery. (3) The posterior pararenal space contains no major organs and consists mainly of blood vessels, adipose tissue and lymphatics, muscles, and nerves. Some have described a fourth space, known as the (4) great vessel space. This area consists mainly of the aorta and inferior vena cava. Organs in the retroperitoneum can be primarily or secondarily retroperitoneal depending on their embryologic origin. Primarily retroperitoneal structures were retroperitoneal during the entirety of development (ex. Adrenal glands, kidney). Secondarily retroperitoneal structures later migrated behind the peritoneum during development (ex. duodenum, colon) [19].

The clinical presentation of RPS differs from that of other sarcomas, such as extremity sarcomas. Patients with RPS present later in their disease course, partly because these tumors can grow in the very large retroperitoneal space to very impressive sizes before vague symptoms occur[20]. At diagnosis, patients with RPS present with a median tumor size of 15cm[8], significantly larger than in the extremity. When symptoms do occur, they are vague and indolent in nature, such as increased abdominal girth, nausea, and early satiety, which can further delay the diagnosis as RPS remains very low in the differential diagnosis due to its rarity. Symptoms can also include neurovascular-related symptoms such as lower extremity edema and neurologic or musculoskeletal symptoms such as decreased sensation, tingling, burning, pain, or weakness, due to compression of the femoral nerve. Paraneoplastic phenomena, such as hypoglycemia, have also been described with leiomyosarcomas, and this has been attributed to endogenous production of insulin-like growth factor 2 (IGF-2)[21]. Distant metastases, which occur most commonly to the lung and liver, are present in 10 percent of patients at diagnosis[22] and are more common in certain histopathologic subtypes such as LMS and UPS.

The clinical presentation of RPS differs from that of extremity sarcoma which occur in more superficial, clinically apparent locations. The most common presentation for extremity sarcoma is a painless lump[23], which is clinically detectable on physical exam. Median size of extremity sarcoma at diagnosis is smaller than for RPS, estimated at 10cm and 11cm for soft tissue and bone sarcoma, respectively[24].

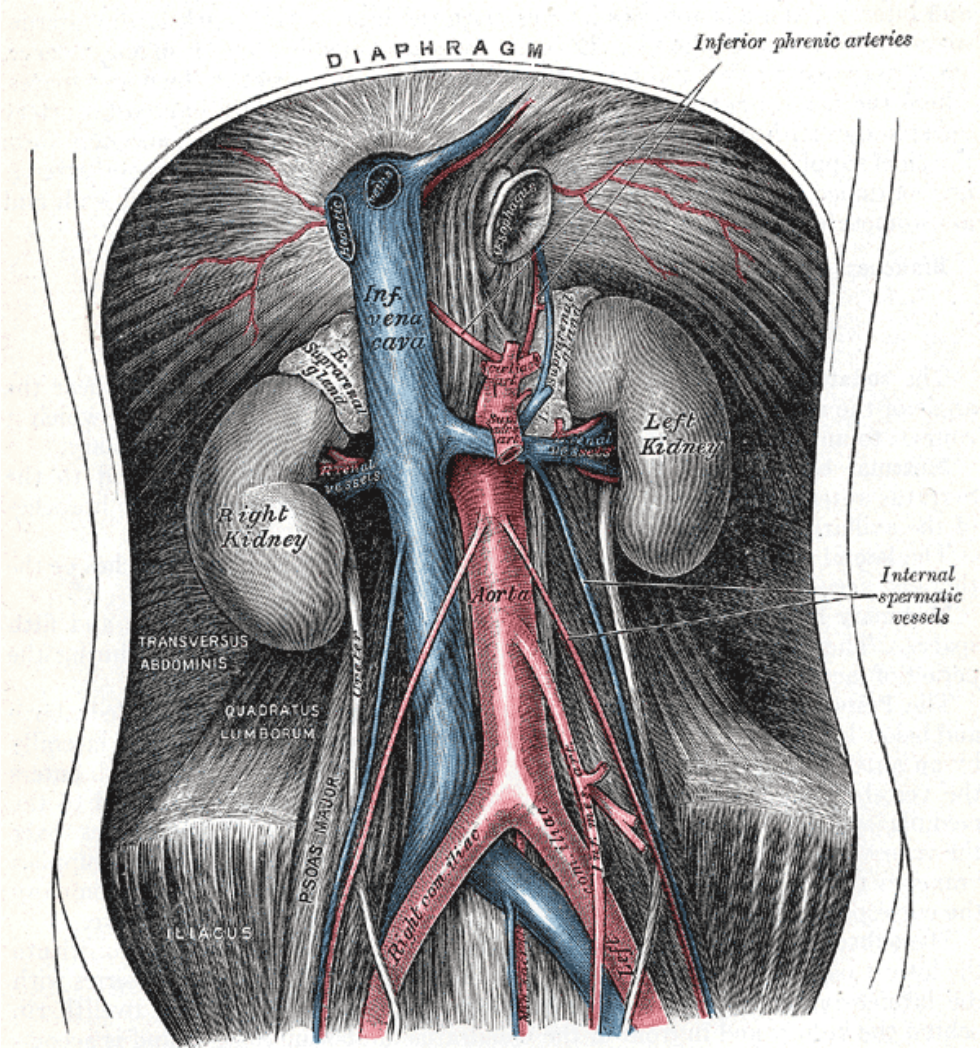

Figure 1.1: Anatomy of the Retroperitoneum, Gray's Anatomy (20th Edition)[25]

1.3 Staging and Diagnosis of Retroperitoneal Sarcoma

The indolent course and vague symptoms in RPS present a diagnostic challenge in the undifferentiated patient[26]. As such, patients are commonly diagnosed from incidentally discovered abdominal masses from imaging studies. In the past decade we have noticed an increase in the diagnosis of RPS due to more liberal use of computed tomography (CT) scans in the emergency department and primary care setting.

Staging for RPS is based on the American Joint Committee on Cancer (AJCC) classification. Based on the most recent edition (8th edition), staging for STS is complex as there are over 50 histologic subtypes and many anatomic considerations. The AJCC 8th edition has placed greater emphasis on the anatomic primary site, with 4 major anatomic areas for staging: (1) extremity and trunk, (2) retroperitoneum, (3) head and neck, and (4) visceral sites.

Since many subtypes of sarcoma are difficult to distinguish from imaging studies alone, tissue diagnosis becomes an important aspect of diagnostic evaluation[26]. The histologic grade is determined by taking a biopsy of the mass and looking at the tissue under the microscope, taking note of specific elements to determine grade which will be highlighted later. In terms of biopsy recommendations, the Trans-Atlantic RPS Working Group (TARPSWG), a transatlantic collaboration of multiple specialized sarcoma centers recommends multiple large core needle biopsies (14-16 Gauge) in order to increase diagnostic yield[26]. There is increasing data demonstrating that image directed biopsy improves the yield in terms of both grade and histologic subtype of the RPS[27]. Indeed, the concordance in histologic subtype and grade in tertiary care center are only 67%[28]. There were previous concerns that biopsy of RPS may lead to tumor tract seeding (spreading of tumor cells along the biopsy tract), however, previous studies demonstrated that there is only a negligible risk of tumor tract seeding[26,29,30].

Histologic grade for RPS is determined according to the Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grading system, which is composed of three major categories: (1) Tumor differentiation, (2) Mitotic count, and (3) Necrosis[31]. When referring to the histologic subtype/differentiation, this refers to taking part of the tumor under a microscope to determine the composition of the RPS and the differentiation of the tumor (or how closely the

tumor cells resemble the cells from where the cancer originates. For example, liposarcoma is a sarcoma which develops from adipose (fat) tissue. A well differentiated liposarcoma refers to resembling the normal adult mesenchymal tissue. A poorly differentiated tumor is one where cells look very abnormal when compared to the normal tissue's cell shape, nucleus, color, or size.

Mitotic count is also an important part of determining tumor grade. Mitotic count is a measure of how fast RPS cells are dividing. This is generally calculated by looking at 10 high-power fields (HPF) under a microscope. In general, the higher the mitotic count, the more cells are identified in mitosis suggesting a higher rate of cell division and tumor growth.

The last component of the FNCLCC grading for STS is the presence of necrosis which is also suggestive of rapid tumor growth. With rapid tumor growth, the tumor grows at a rate faster than adequate vascularization could be provided to supply nutrients to the tumor. This leads to significant metabolic stresses from elements such as hypoxia and inadequate glucose supply to the tumor[32]. Presence of tumor necrosis is generally associated with poorer prognosis.

Differentiation Score	Definition
1	Sarcomas closely resembling normal adult mesenchymal tissue
2	Sarcomas for which histologic typing is certain
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count Score	Definition
1	0–9 mitoses per 10 HPF
2	10–19 mitoses per 10 HPF
3	≥ 20 mitoses per 10 HPF

Tumor Necrosis Score	Definition
0	No necrosis
1	< 50% tumor necrosis
2	≥ 50% tumor necrosis

FNCLCC Histologic Grade	**Grade Definition**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 - 3
G2	Total differentiation, mitotic count and necrosis score of 4 - 5
G3	Total differentiation, mitotic count and necrosis score of 6 - 8

Table 1.1 - American Joint Committee on Cancer 8th Edition, Soft Tissue Sarcoma FNCLCC Grade[31]

Clinical Staging using the TNM staging - tumor (T), nodes (N), metastasis (M), and grade (G) is less popular in RPS. T refers to the tumor size, which is measured in the largest diameter. Tumor size criteria varies by anatomic location. N refers to cancer involvement in lymph nodes, however nodal involvement is generally rare in adult STS. T and N can be used to determine if a cancer is locally advanced. M refers to any metastases of the primary malignancy to other organs, such as the lungs[31]. The G criteria refers to the FNCLCC score.

It is important to note, however, that the FNCLCC grade and TNM stage do not necessarily take the many histologic subtypes of RPS or the completeness of resection into consideration, which have significant prognostic implications for the patient. As such, a multi-institutional nomogram which has been validated in multiple studies[33,34] was created called the Sarculator. The Sarculator is available as a mobile app and provides nomograms for DFS and OS for both RPS and extremity STS. For example, for primary RPS, the Sarculator provides a 7-year DFS and OS after providing information on patient age, tumor size, FNCLCC grade, histologic subtype, multifocality and completeness of resection.

Like most malignancies, RPS will require imaging studies for operative planning and staging. Staging is the process in which the extent of disease is ascertained through histologic and radiologic testing. The stage often tells us how far advanced the patient's disease is and if the patient is a surgically resectable with curative intent. For all RPS, magnetic resonance imaging (MRI) is the recommended exam for primary tumor staging. However, Computed Tomography (CT) infused with intravenous contrast can provide similar information if MRI is unavailable with some exceptions. For example, MPNST is better delineated in MRI as MRI can determine the mass's relationship with the nerve and can delineate involvement of adjacent

structures for surgical planning[35]. In RPS with metastatic potential, a CT scan of the chest is necessary to rule out metastatic disease. In sarcomas which have a higher likelihood to spread to lymph nodes, sentinel lymph node mapping via scintigraphy can be performed. Following this, staging images depend on the histologic subtype of the RPS. For example, in round cell liposarcoma, a higher risk of bone marrow metastases is expected, and therefore MRI of the spine and pelvis to rule out marrow metastases is recommended.

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has also been increasingly used in management of RPS. The role of PET scans has not been clearly defined in guidelines, however, studies have shown a strong correlation between standardised uptake value (SUV) and tumour grade, suggesting a way to differentiate low- and high-grade sarcomas, including liposarcoma, leiomyosarcoma, and MPNST[36]. FDG-PET/CT may also be used to differentiate WDL and DDL which can help with increasing diagnostic yield with percutaneous biopsy[37] as areas of dedifferentiation can be difficult to detect on CT alone.

1.4 Management of Retroperitoneal Sarcoma

The management of RPS is complex and requires the expertise of a multidisciplinary team in a sarcoma referral centre[38,39]. These referral centres are often tertiary or quaternary care centres with specialists and the infrastructure necessary to safely and successfully treat these patients. The specialists include but are not limited to surgical, medical, and radiation oncologists as well as radiologists and pathologists all specialized in the treatment of sarcoma.

The cornerstone of treatment, and the only chance for cure in RPS is with surgical resection. In order to obtain negative margins (R0 and R1 resections are generally considered

negative margins in RPS), multivisceral resections (resecting multiple organs and other areas adjacent to the mass not necessarily invaded by the cancer) are often required. Multivisceral resection has been shown to reduce local recurrence rates compared to excising the sarcoma alone, through the mechanism of reducing likelihood of positive margins[40].

Centralizing care for illnesses involves referring patients for a particular illness to limited treatment centres, in which the illness in question will be managed almost exclusively by the referral centre. In the last 2 decades, there has been ample evidence supporting centralized cancer care for malignancies including but not limited to esophageal, pancreatic and colon cancer. It is suggested that increased volumes, particularly for less common illnesses, and access to a referral centre with a multidisciplinary team are associated with improved outcomes[41-43]. Following this, studies have also demonstrated that treatment at specialized sarcoma centers is associated with higher likelihood of resection and improved surgical outcomes, defined as increased overall survival, higher likelihood of undergoing surgical management, and higher rates of R0/R1 resection in RPS[44-47]. Referral at high-volume centers were also associated with higher receipt of non-surgical treatment such as radiation therapy and chemotherapy, which can improve overall survival and quality of life[48].

Histologic subtype for RPS is an important prognostic indicator as it gives information on disease aggressiveness as well as behavioral patterns such as local organ involvement in WDL versus preponderance of metastatic disease in LMS[49]. Histologic subtype of RPS is a good predictor for local and distant recurrence as well as a strong predictor of disease-specific mortality[50,51] and overall survival[52]. For example, using the Sarculator, a 50-year-old patient with

a 10cm grade 2 WDL with R0 resection has a 7-year OS of 51%, whereas changing the histologic subtype to LMS would be associated with a 7-year OS of 72%.

As an example of the importance of histologic subtype in management of RPS, liposarcoma has the highest rate of local recurrence. Visually, liposarcoma, and in particular well-differentiated liposarcoma, is also very difficult to differentiate from normal fat. This difficulty in differentiating non-diseased and diseased tissue challenges a negative margin in surgery. Therefore, one would expect a more extensive surgery in this histologic subtype to maximize chances for negative margins. In fact, the goal of surgery for this pathology in RPS requires removal of essentially all retroperitoneal fat on the same side of the RPS whereas LMS would be more clearly distinguishable from retroperitoneal fat and may not require extensive excision of all ipsilateral retroperitoneal fat[26].

Determination of surgical candidacy in a patient with RPS is complex and multifactorial. When discussing surgery with patients, the surgeon must first decide if surgical resection for RPS is indicated. Even if surgery is technically feasible, this is only part of the overall decision to offer surgical resection for RPS. If indicated, patient factors, such as overall health, physical function, and mental status must be taken into consideration as these factors can affect patient recovery, complications, and peri-operative mortality[53]. Other contraindications to surgery related to anatomical considerations include but are not limited to involvement of both kidneys, spinal cord involvement, and complete involvement of the superior mesenteric artery, the celiac axis and porta hepatis, blood vessels or areas containing important blood vessels of critical importance which supplies blood to the majority of the gastrointestinal organs[26].

Important surgical and oncologic principles in RPS cannot be highlighted enough. This includes adequate exposure in the operating room to be able to properly assess the extent of tumor involvement as sometimes imaging can underestimate the true involvement of the tumor. This includes a generous laparotomy, a vertical incision in the midline of the abdomen, surveying the abdomen for any evidence of sarcomatosis, proper mobilization of intra-abdominal organs and tissue to expose the retroperitoneum and the specific area where the primary tumor lies. Next, the surgeon assesses which organs, blood vessels or other tissues must be resected en-bloc. This sometimes requires the expertise of other surgical subspecialties, such as vascular surgeons, to increase the chances of negative margins. The kidney and the colon are the most commonly resected organs, which are removed in 28-55% of patients with RPS[50,51].

Patients with RPS may be offered non-surgical treatments, such as chemotherapy and radiation therapy, which may be used in conjunction with surgery or can be offered to patients who are not surgical candidates (palliative treatment), however, these treatments are not standardized and should be discussed with a multidisciplinary team. The role of radiation therapy in the neoadjuvant setting (treatment given prior to surgery to decrease the size of the primary tumor and increase likelihood of negative margins) is not clear. A study published in 2016 by Nussbaum et al showed that neoadjuvant radiotherapy (HR 0·70, 95% CI 0·59-0·82; p<0·0001) and adjuvant (treatment after surgery) radiotherapy (HR 0·78, 0·71-0·85; p<0·0001) were significantly associated with improved overall survival compared with surgery alone in a case-control, propensity score-matched analyses of 9068 patients[54]. However, the STRASS trial, published by Bonvalot et al in 2020, was the first international randomized control trial assessing the impact of neo-adjuvant radiation on oncologic outcomes in RPS, which included 266 patients

with localized RPS who were randomized to either surgery alone or neoadjuvant radiation with surgery and showed no difference between the two groups (hazard ratio 1·01, 95% CI 0·71-1·44; log rank p=0·95)[55]. However, twice as many patients in the surgery alone group had local recurrence compared to the neoadjuvant radiation and surgery group. In addition, in post-hoc sensitivity analysis, when looking at the liposarcoma subgroup alone, there was some signal of improved abdominal recurrence free survival with neoadjuvant radiation and surgery (hazard ratio 0·62, 95% CI 0·38–1·02).

The use of systemic therapy such as chemotherapy is also controversial. The standard first-line chemotherapy for soft tissue sarcoma is doxorubicin or doxorubicin/ifosfamide, however this varies depending on histologic subtype. Most studies looking at neo-adjuvant chemotherapy in STS have low numbers of patients with RPS or have excluded RPS entirely from their analysis. Therefore, the effects of neoadjuvant chemotherapy and oncologic outcomes in RPS has not been well studied. Recently there have been several new systemic therapies as well as immunotherapies that have shown efficacy in specific histologic subtypes in STS, the benefit of which has yet to be determined in the neoadjuvant and adjuvant setting for RPS[56].

1.5 Distance decay as a prognostic risk factor

Inequality in access to health care services is a critical concern for health policymakers. Patients living in rural areas often travel greater distances to access various healthcare services[48]. In addition, healthcare services offered in rural regions often provide limited services and still require traveling further away to require more care for more complex cancers. In addition to traveling longer distances, patients living in rural areas have to endure extreme weather,

challenging road conditions, and reduced access to transportation, all factors which contribute to the difficulty for rural residents to access certain healthcare services[57].

The adoption of centralized care can lead to an increase in the patient's travel burden as fewer hospitals can provide care for illnesses managed through referral centres. With increasing travel times, an important concept to consider is the distance decay effect. The distance decay effect is defined as an association between patients living closer to healthcare facilities and increased utilization of healthcare services and/or better health outcomes[48,58]. Studies have shown that factors affecting spatial interactions between patients and healthcare services can include a patient's age, health insurance, gender, race, education level, and socioeconomic status[59-62]. Conversely, the distance bias effect, where patients who live further away from a health centre have improved health outcomes or access to healthcare resources, has also been described. The rationale for the distance bias effect is one where a self-selection of patients can travel further from factors including better baseline health, referral bias, or higher socioeconomic status[48,63,64].

The distance decay effect has been described as early as the 1800's, when Dr. Edward Jarvis first noted that fewer patients were admitted to a psychiatric ward the further away they lived from the hospital[65]. Some evidence suggests that this relationship persists today, with increased distance from a psychiatric health facility being associated with decreased caseloads the further away patients live for both inpatient wards and outpatient clinics[66] as well as a trend of increased travel distance for patients who require subspecialty psychiatric care[67].

A distance decay effect has been suggested in oncology as well. For example, when looking at all cancer mortality-to-incidence ratio for each health region from Statistics Canada,

Chan et al have demonstrated an association between increased distance to radiation oncology services and poorer cancer outcomes[68]. In 2019, a retrospective cohort study of 2599 patients was published comparing patients treated for RPS at long-distance high-volume hospitals to short distance low volume hospitals in the USA[69], however, this paper focused on outcomes related to centralization of care and not the impacts of travel distance alone on oncologic outcomes in RPS.

To our knowledge, no specific studies have assessed the phenomenon of distance decay for RPS or its impact in a single payer model, such as in the Canadian healthcare system. Given the heterogenous population density in Canada, some patients must travel long distances to access healthcare services. These distances are likely increased with having to travel to referral centres for specific treatments, as is the case with sarcoma treatment in general. With this in mind, we hypothesized that patients who lived further away from a referral centre that treats RPS would have poorer oncologic outcomes.

Chapter 2 – THESIS OBJECTIVES

As a primary objective for this thesis, we aimed to compare oncologic outcomes (DFS, PFS, and OS) between patients living in the census metropolitan area where a designated sarcoma center exists and the rest of the province.

Chapter 3 – THESIS MANUSCRIPT

3.1 Introduction to thesis manuscript

RPS is a rare malignancy for which specialized care in referral centers is necessary for optimal treatment. With this realization, treatment in specialized care has led to a shift in referral, where care for RPS is centralized to only select hospital centres which contain the experience and expertise from a multidisciplinary team of specialists and allied healthcare professionals. This, in turn, may offer more consistency in care, have the resources available for management of this disease, and can enroll and expose patients to clinical trials for further disease control and to add to the current body of literature for this rare illness which will benefit patients diagnosed with RPS in the future.

Symptom onset can occur late in the disease process of RPS and with centralization of care for RPS, patients may have to travel longer distances to access care for RPS, which may further delay initiation in treatment. As such, patients may present with more advanced disease and in organizing tests and appointments while living further away, may experience delays in receiving important tests or treatments necessary for the management of this illness. With this in mind, we hypothesized that increased distance from a sarcoma referral centre may translate to worsening oncologic outcomes in RPS.

To our knowledge, there is no data in the literature which studies the relationship of distance from a sarcoma referral centre and oncologic outcomes in RPS. Therefore, the objective of this manuscript was to investigate the relationship of distance on oncologic outcomes in RPS.

3.2 Manuscript

Does increased distance from specialized cancer care affect outcomes? An analysis of geographic inequalities in patients with retroperitoneal and intra-abdominal sarcomas.

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ABSTRACT

BACKGROUND

Retroperitoneal sarcomas (RPS) are rare malignancies requiring specialized care in referral centres. With late symptom onset and only select centres providing treatment, do patients living farther away have worse outcomes? This study's objective was to compare outcomes between patients with RPS living within and outside the census metropolitan area (CMA) of a sarcoma referral centre.

METHODS

A retrospective study of patients with RPS seen at a sarcoma referral centre from 2008-2019 was performed. Patients were separated into "metropolitan area" (MA) group if they lived within the CMA of the sarcoma referral centre and "outside the metropolitan area" (OMA). Cox regression analysis was used to compare hazard ratios for Disease-Free Survival (DFS), Progression-Free Survival (PFS) & Overall Survival (OS) between groups.

RESULTS

101 patients were included (MA: n=78, OMA: n=23). Cohorts were compared across baseline demographics. Average Euclidian distance was significantly different for MA vs OMA (15.21 vs 187.05 km, SMD = 1.623). In our multivariate analysis, patients in the OMA group were associated with worse PFS (HR:3.50, 95CI:1.14-10.75, p=0.029) & OS (HR:2.10, 95CI:1.05-4.23, p=0.037). OMA group had longer time to initiating neoadjuvant radiation (133.60 vs 61.55 days, SMD=0.445) & undergoing biopsy from consultation (64.60 vs 17.94 days, SMD=1.013).

CONCLUSION

This study suggests decreased PFS & OS in patients with RPS living farther away from a sarcoma referral centre. This is the first study suggesting a distance decay effect in RPS.

Further studies are needed to understand which modifiable components of care from increased distance contribute to worse outcomes.

Synopsis

Management of retroperitoneal sarcomas requires the expertise of a multidisciplinary team, in which some patients must travel long distances to access specific healthcare services. This study looks at distance as a risk factor for worsening oncologic outcomes in retroperitoneal sarcoma.

INTRODUCTION

Soft tissue Sarcomas (STS) account for less than 1% of all adult cancers and most commonly occur in the extremities [1]. Retroperitoneal sarcomas (RPS) and intraperitoneal sarcomas (IPS) consist of 20% of all STS [2]. At presentation, RPS are often large, involving adjacent organs and vital structures. Management for this malignancy is complex and requires the expertise of a multidisciplinary care team in a sarcoma referral centre [3-5]. These are often tertiary or quaternary care centres with specialists and the infrastructure necessary to safely and successfully treat these patients. Surgery is the cornerstone of curative treatment. In the United States, 19,750 new cases of STS were reported, with 3,044 cases of retroperitoneal and intraperitoneal origin [6]. According to Statistics Canada, the incidence is 1150 new Canadian cases of soft tissue sarcomas, 255 of those being diagnosed in Quebec [7].

In recent years, attempts have been made to centralize the care of malignancies including esophageal, pancreatic, and colorectal cancer as increased volumes and access to multidisciplinary teams are associated with improved outcomes [8-10]. Centralization of care for RPS has been shown to improve overall outcomes for patients through mechanisms of increased volume of cases for physicians, multidisciplinary treatment from dedicated sarcoma trained specialists with access to tumour boards, inscription in sarcoma databases, and involvement in clinical trials [8].

Multiple studies have demonstrated that treatment at specialized sarcoma centres is associated with higher likelihood of resection and improved surgical outcomes, defined as increased overall survival, higher likelihood of undergoing surgical management, and higher rates of R0/R1 resection in RPS [11-14], all quality benchmarks for RPS. In addition, high-

volume centres were associated with higher receipt of radiation therapy and chemotherapy, which can lead to improved outcomes [15].

Geographic factors, such as distance from a health centre, have an impact on health outcomes for certain diseases, particularly in vulnerable patient groups [16]. With the adoption of centralized care, a patient's travel burden often increases as less hospitals can provide care for specific, complex diseases [17,18]. With increases in travel time, an important consideration is the distance decay effect defined as an association between patients living closer to the healthcare facility having better health outcomes [15,19]. Conversely, a distance bias effect has also been described; a phenomenon where patients who live farther away from a health centre have better health outcomes. The latter effect can potentially be explained by a self-selection of patients able to travel longer distances having better baseline health, referral bias, or higher socioeconomic status [15,20,21].

Several studies have supported a distance decay effect in cancer care. Virgilsen et al demonstrated that a longer distance to cancer-diagnostic facilities was associated with increased odds of advanced tumour stage at diagnosis for melanoma, rectal, testicular, and cervical cancer[22]. Furthermore, when looking at all cancer mortality, Chan et al have shown an association between increased distance to radiation therapy and poorer cancer outcomes[23]. In extremity sarcoma, Moten et al demonstrated that patients who travelled at least 15 miles had larger tumours, higher odds of stage II compared to stage I disease (OR, 1.14; 95% CI, 1.04-1.24), longer median time to initiation of treatment or requiring more extensive surgery[24].

Distance from a sarcoma centre for patients has increased in the last decade given strong recommendations that RPS management should be centralized[3,9,14,25-27]. As such, does a

distance decay relationship exist for patients with RPS? A recent study demonstrated that traveling to high-volume centres for RPS treatment conferred a significant short and long-term survival advantage, however, this was a study supporting centralized care for RPS and not about the effects of distance on health outcomes[28]. To our knowledge, no specific studies have assessed the distance decay effect on oncologic outcomes for RPS or its impact in a single payer model, such as in the Canadian healthcare system.

Given the heterogenous population density in Canada, which include areas with low population density, some patients must travel long distances to access certain healthcare services. These distances are likely increased with having to travel to referral centres for specific treatments, as is the case with sarcoma treatment in general. As such, we hypothesized that patients who lived farther away from a sarcoma referral centre would have poorer oncologic outcomes. As a primary objective, we compared overall survival (OS) between patients living in the census metropolitan area where a designated sarcoma referral centre exists and the rest of the province [29]. As a secondary objective, we compared Disease-free survival (DFS) and progression-free survival (PFS).

METHODS

Study design

We conducted a single-centre, retrospective cohort study of all patients seen in consultation for RPS and IPS from the McGill University Health Centre (MUHC) between 2008-2019. Our institution is one of four designated centres of sarcoma excellence in Quebec, Canada for management of all sarcomas with a catchment area that spans across the entire province. After ethics approval, a patient list was obtained from our institution's Cancer Registry using

ICD-10 codes for Malignant neoplasms of retroperitoneum (C48.0) and Malignant neoplasms of overlapping sites of retroperitoneum and peritoneum (C48.8) to identify patients.

All procedures were performed by board certified surgical oncologists overseeing the care of retroperitoneal and intraperitoneal sarcomas. Patients who received the majority of their care outside our institution, patients under 18, patients with a synchronous malignancy diagnosed, patients with extremity, abdominal wall, chest, head and neck sarcomas were excluded from the study. Patients who died within 30 days of treatment initiation were also excluded from the study. These patients were excluded to focus on oncologic survival outcomes and mortality from surgical complications or other treatment adverse events.

Metropolitan Area group and Outside Metropolitan Area group

A census metropolitan area (MA) is defined as an area consisting of one or more neighbouring municipalities surrounding a major urban core, with a total population of at least 100,000 with 50,000 or more living in the urban core[29]. Patients living outside of the MA group for the Greater Montreal area were placed in the outside census metropolitan area (OMA) group. Patients attributed to the MA and OMA groups were based on the address on file at time of primary consultation with a sarcoma specialist. Home and hospital addresses were geocoded and converted to latitude and longitudinal coordinates. These coordinates were imported into ArcGIS (Desktop version 10.7.1, Esri inc., Redlands, CA, USA) and a Euclidian (straight line) distance between patients' residential address at time of consultation and the sarcoma referral centre was calculated for each patient.

Patient characteristics and outcomes

Patient baseline characteristics, such as age, sex, and Charlson comorbidity index, as well as clinical, pathological, and perioperative information was collected from review of the

electronic medical record (EMR). Clinical details collected included pertinent comorbidities, histopathological characteristics of biopsy results, treatments received, peri-operative course, dates of visit with members of the multidisciplinary team including surgical, medical and radiation oncologists. Time to diagnostic tests or interventions was calculated from the initial consultation with surgical oncologist. Time to staging was calculated from the dates of the first and last imaging modality needed to stage the patient at the surgeon's discretion.

Our outcomes of interest were DFS, PFS, and OS. Disease recurrence for RPS and IPS was defined as radiologic evidence of disease following surgical resection of the sarcoma and was further divided into local recurrence and distant recurrence. Follow-up imaging was assessed using a provincial-wide imaging record system. In patients undergoing surgical resection, DFS was calculated using the date of radiological recurrence, administrative end date (if no evidence of recurrence), or death (if death occurred without evidence of recurrence) and the date of surgery. PFS was calculated using the date of radiologic evidence of disease and the date of radiologic evidence of disease progression. OS was calculated using date of date of radiologic diagnosis and the date of last follow-up or date of death.

Data Analysis

Standardized mean difference (SMD) was used to compare categorical variables and means of continuous variables [30]. Cox regression analysis was used to compare DFS, PFS and OS, controlling for age category and histological subtype. Kaplan-Meier curves were generated for DFS, PFS, and OS and log rank test was used to compare the differences between the survival curves. A hazard ratio with 95% confidence intervals is generated with corresponding p-values (significance if $p < 0.05$). Statistical analyses were performed using RStudio (version 1.2.1577; RStudio, Inc., Boston, MA, USA).

RESULTS

Study Group

A cohort of 139 patients were identified who were treated for RPS and IPS from 2008-2019. After excluding 38 patients from the study (22 patients received the majority of their treatment outside of our institution, 14 patients died within 30 days of treatment initiation, 1 patient had a synchronous second malignancy diagnosed, and 1 patient had an unconfirmed diagnosis), a total of 101 patients were included in the study. Baseline characteristics between groups are listed in table 1. Seventy-eight patients lived in the census metropolitan area and were included in the MA group while 23 patients lived outside of this area and were included in the OMA group.

The average age was 61 years and 50.5% of patients were female. The most common histologic subtype was dedifferentiated liposarcoma in 35.6% of patients. Twenty-eight percent of patients received neoadjuvant radiation and 74% underwent surgical resection. Straight line distance differed significantly between groups and was lower in the MA group (mean:15.2km (SD:11.2km) vs 187.1km (SD:149.3km), SMD:1.623). Histologic subtype differed between groups (SMD:0.488). Patients who underwent neoadjuvant radiation (28.2% vs 26.1%, SMD:0.048) or surgical resection (75.6% vs 69.6%, SMD:0.137) were comparable between groups. Patients in the OMA group were almost twice as likely to present with metastatic disease (MA:11.8% vs OMA:22.7%, SMD:0.291).

The biggest delays to care (Table 2) from patients in the OMA group were to core biopsy (MA:17.9 vs 64.6 days, SMD:1.013) and to initiation of neoadjuvant radiation (MA:61.6 vs 133.6 days, SMD:0.445). Time to surgery was comparable between groups (MA:105.7 vs 101.1 days, SMD 0.033).

Surgical Details and Oncologic Outcomes

As shown in table 3, 75 patients underwent surgical resection (MA:59 (75.6%) vs OMA:16 (69.6%), SMD:0.137) while 32 patients underwent nephrectomy (MA:47.5% vs OMA:25%, SMD:0.481). Multi-visceral resection was performed in 37 patients who underwent surgical resection (MA:50.8% vs OMA:43.8%, SMD:0.143). Recurrences were comparable between groups (MA:37.2% vs OMA:39.1%, SMD: 0.04).

Overall, all oncologic outcomes were higher in the group that lived in the same census metropolitan area as the referral centre. DFS was higher in the MA group by 7.8 months (MA:35.8 months vs. OMA:28 months, SMD 0.270). PFS was significantly higher in the MA group by 10.1 months (MA:16 months vs. OMA:5.9 months, SMD 0.794). Overall survival was also significantly higher in the MA group by 14 months compared to the OMA group (MA:44.5 months vs. OMA:30.2 months, SMD 0.430).

Kaplan-Meier Survival curves are shown in Figure 1 comparing DFS, PFS, and OS between MA and OMA groups. DFS was not significantly different in the KM curves (log-rank: p=0.44). Although PFS curves had early cross-over, it demonstrates superior PFS for patients in the MA group with statistical significance (log-rank: p=0.018). OS, although not statistically significant (log-rank: p= 0.063), signalled towards increased OS for patients in the MA group. Patients in the OMA group had a poorer PFS in the univariate analysis (HR:3.39 (95% CI:1.17-9.84), p=0.025) and after adjusting for age and histologic subtype in the multivariable analysis (HR:3.50 (95% CI:1.14-10.75), p=0.029). OS was not statistically significant in the univariate analysis (HR:1.89 (95% CI:0.96-3.73), p=0.067), however, there is a strong signal for lower OS in the OMA group with statistical significance in the multivariable analysis, after adjusting for age and histologic subtype in OS (HR:2.10 (95%

CI:1.05-4.23), p=0.037). For DFS, the "other" histologic subtype was the only variable significantly associated with recurrence in both the univariate (HR:8.93 (95% CI:2.26-35.36), p=0.002) and multivariable (HR:8.95 (95% CI:2.26-35.53), p=0.002) analysis (Table 4).

DISCUSSION

To the best of the authors' knowledge, this is the first study to suggest a distance decay effect in patients with RPS; living outside the boundaries of a sarcoma referral centre's census metropolitan area was associated with worse PFS and OS. DFS was poorer in the OMA group, however this was not statistically significant in our cohort. PFS was, on average, 10 months higher in the MA group, while OS was, on average, 14 months higher in the MA group. The most common histology in this cohort was DDL, with most resections considered complete resections (R0 or R1 Resection). Around half of the cohort underwent multi-visceral resection. Despite the paucity of data available for RPS, these findings are comparable to previous studies[31,32]. In addition, this study demonstrated that aspects of a patient's care for RPS may be delayed further with increased distance to a sarcoma referral centre.

The effect of distance to treatment centres on outcomes has been studied in other disease processes. When looking at distance decay, one of the factors to take into consideration is how distance is calculated in each study. Kelly et al. analysed 108 studies of varying pathologies and treatments in a systematic review looking at health outcomes and travel distance or travel time[15]. The methods used to assess travel were straight line distance (or Euclidian distance), travel time, or road network-based distance.

Calculating distance can be challenging as travel times can be affected by many factors. In our study, given that seasonal variation and traffic density depending on time of day would

significantly affect travel time, this would make comparing travel times between patients difficult to interpret. In a similar vein, using road-network-based distance in this study was difficult to interpret given that the sarcoma referral centre was relocated to a different borough in 2015 with significant construction around this hospital centre causing multiple changes in road distance and traffic density which would alter the spatial accessibility to these health services. In addition, several studies have suggested that travel time or road network distance were highly correlated with Euclidian distance, making it a good estimate to compare distances[33,34]. As such, Euclidian distance offered the most consistent measurement of distance when compared to road network distance and travel time. Some studies used the nearest hospital instead of the hospital of treatment [15]. Given that the nearest hospital may not necessarily be the hospital in which patients go to receive care, with data supporting that less than 40% of patients requiring specialty care actually visited the nearest hospital[35], using the nearest hospital would vastly underestimate the distance travelled by patients.

Outcomes have also been compared between patients living within and outside metropolitan areas[36-38]. Rural communities are notoriously underserved when it comes to medical services. Baade et al demonstrated that 5-year survival outcomes for prostate cancer were lower in rural areas when compared to urban areas in Australia[36]. Henley et al's work suggested that non-metropolitan areas had higher incidence of and deaths from several cancers which can be prevented by screening. These differences in cancer death rates might reflect disparities in access to health care and timely diagnosis and treatment.

We were interested in comparing MA and OMA as the sarcoma referral centre in this study is located in a metropolitan area and that, in general, patients living in non-metropolitan

areas travelled much longer distances. We felt that dividing patients into CMA groups and comparing them to patients living outside of this area would make our findings more generalizable to other countries where total distance travelled by patients may be smaller. In addition, given the relatively small size of the island of Montreal and the sarcoma referral centre being used by many patients living outside of this area, we did not think that the distance decay effect would be apparent if only looking at the island of Montreal alone. Using the census metropolitan area definition, we were able to divide patients who lived in and outside of one specific census metropolitan area of which the sarcoma referral centre is located.

In this study, patients in the OMA group, on average, lived further away from the sarcoma referral centre than patients in the MA group. Dividing patients into MA and OMA groups had different number of patients per group (78 vs 23 patients, respectively). Given that we would expect higher population densities in metropolitan areas, it was expected that fewer patients would be included in the OMA group. The small sample size in this cohort limited the use of straight-line distance as a categorical variable. Converting straight line distance into categorical variables (ex. Closest to vs further away from referral centre) was difficult to interpret since the values between the furthest straight-line distance in the group closest to the referral centre and the closest distances in the group further from the referral centre were similar in value. In addition, given that there are no established criteria in the literature for RPS which designates a sarcoma centre as "far", this limited our use of straight line-distance.

While the tumour biology and management of RPS are distinct from other malignancies including extremity sarcoma, our findings are comparable with other studies suggesting a

distance decay effect. In our cohort, patients in the MA group had a longer PFS and OS. Patients in the OMA group were more likely to present with metastatic disease, be offered palliative chemotherapy or radiation therapy for unresectable disease and have significant delays to initiation with neoadjuvant radiation. Neoadjuvant radiation is usually performed over several weeks and can require temporary lodging for patients living far away, which may require advanced planning and contribute to the delay seen in our study. Of note, there was no difference between groups for time to surgery from initial consultation with a surgical oncologist. Overall, these findings support a distance decay effect for RPS, and patients who live outside of the sarcoma referral centre's census metropolitan area have worse health outcomes as well as delays to components of their management.

There were some limitations inherent to the study design that merit further discussion. This was a retrospective single centre study looking at an uncommon disease. The small sample size from the study, while comparable to other studies in RPS, may also affect the precision of the outcomes calculated. This study adjusted for age and histologic subtype, covariates which are commonly adjusted for in RPS models. Models for RPS usually adjust for Resection type (R0/R1 vs R2) as well but given low frequency of R2 resection in our patient population we did not feel this provided additional strength to the model.

Another limitation in this study is the interpretation of increased distance from a sarcoma centre by comparing patients who live within and outside the metropolitan area of a sarcoma referral centre. While patients in the OMA group did have a higher Euclidian distance than patients in the MA group, there may be other factors acting as confounders related to living outside of a metropolitan area which can contribute to the worse oncologic outcomes in the

OMA group. This includes but is not limited to socioeconomic status and proximity to healthcare services such as clinics, emergency rooms or family physicians.

What remains unclear, and what would help with measures to address this inequality, would be to better understand if delays to treatment initiation affect oncologic outcomes in RPS. We suspect that this would vary with histologic subtype, however we believe our study was underpowered to truly assess delays to initiation of treatment between these two groups. This would be useful in looking at the development of multidisciplinary clinics where patients can meet with all members of the multidisciplinary team to reduce any delays in therapy between appointments and multidisciplinary visits. Moreover, if delays in certain parts of care are identified, such as undergoing biopsy for tissue diagnosis or initiation of treatment, efforts and resources can be redirected to modify these factors. Moving forward, further multi-centre studies should explore distance decay in RPS. Trials looking at multidisciplinary clinics and the impact of delays to care should also be considered.

CONCLUSION

This retrospective cohort studies finds a decrease in PFS and OS in patients with RPS who live further away from a sarcoma referral centre. Further studies are needed to better understand the mechanisms that lead increased distance to be associated with worse oncologic outcomes to develop strategies which will mitigate this inequality including raising awareness amongst medical professional of rare tumours.

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Table 1: Patient demographics and Surgical Details

	MA (n=78)	OMA (n=23)	SMD
Euclidian Distance (mean (SD)) (Median [IQR]) (Km)	15.21 (11.16) 14.0 [12.93]	187.05 (149.28) 164.79 [118.58]	1.623
Age – years (mean (SD))	61.62 (12.37)	58.35 (12.63)	0.261
Sex (Male) (%)	38 (48.7)	12 (52.2)	0.069
Smoker (%)			0.354
Ex-smoker	17 (24.6)	4 (18.2)	
Non-smoker	45 (65.2)	13 (59.1)	
Current Smoker	7 (10.1)	5 (22.7)	
HTN (%)	30 (38.5)	4 (17.4)	0.483
DM (%)	12 (15.4)	3 (13.0)	0.067
ACCI (%)			0.309
0	14 (17.9)	5 (21.7)	
1	15 (19.2)	4 (17.4)	
2	19 (24.4)	8 (34.8)	
3+	30 (38.5)	6 (26.1)	
Histology (%)			0.488
Well Differentiated Liposarcoma	12 (15.4)	2 (8.7)	
Dedifferentiated Liposarcoma	25 (32.1)	11 (47.8)	
Leiomyosarcoma	19 (24.4)	7 (30.4)	
Other	22 (28.2)	3 (13.0)	
Neoadjuvant Radiation (%)	22 (28.2)	6 (26.1)	0.048
Adjuvant Radiation (%)	10 (12.8)	1 (4.3)	0.306
Palliative Radiation (%)	9 (11.5)	5 (21.7)	0.277
Neoadjuvant Chemotherapy (%)	3 (3.8)	0 (0.0)	0.283
Adjuvant Chemotherapy (%)	2 (2.6)	1 (4.3)	0.098
Palliative Chemotherapy (%)	13 (16.7)	7 (30.4)	0.329
Tumour Size (mean (SD))	136.49 (76.47)	154.23 (99.39)	0.2
Surgical Resection (%)	59 (75.6)	16 (69.6)	0.137
Metastatic disease at initial consultation (%)	9 (11.8)	5 (22.7)	0.291

SMD: Standardized Mean Difference; HTN: Hypertension; DM: Diabetes Mellitus; ACCI: Adjusted Charlson Comorbidity Index

Table 2: Average time in days to staging and treatment

	MA (n=78)	OMA (n=23)	SMD
Time to imaging ordered from primary consultation (mean (SD))	33.64 (56.20)	20.67 (16.33)	0.313
Time to staging (mean (SD))	71.65 (79.84)	53.20 (51.31)	0.275
Time to neoadjuvant radiation (mean (SD))	61.55 (50.68)	133.60 (223.25)	0.445
Time to palliative radiation (mean (SD))	55.00 (43.46)	40.00 (14.14)	0.464
Time to initiation of treatment (mean (SD))	61.70 (94.35)	65.27 (130.54)	0.031
Time to surgery (mean (SD))	105.68 (109.75)	101.13 (159.23)	0.033
Time to core biopsy ordered from primary consultation (mean (SD))	17.94 (12.04)	64.60 (64.05)	1.013
Time to PET scan (mean (SD))	34.26 (36.13)	24.83 (18.08)	0.33

Table 3: Surgical Details and Oncologic Outcomes

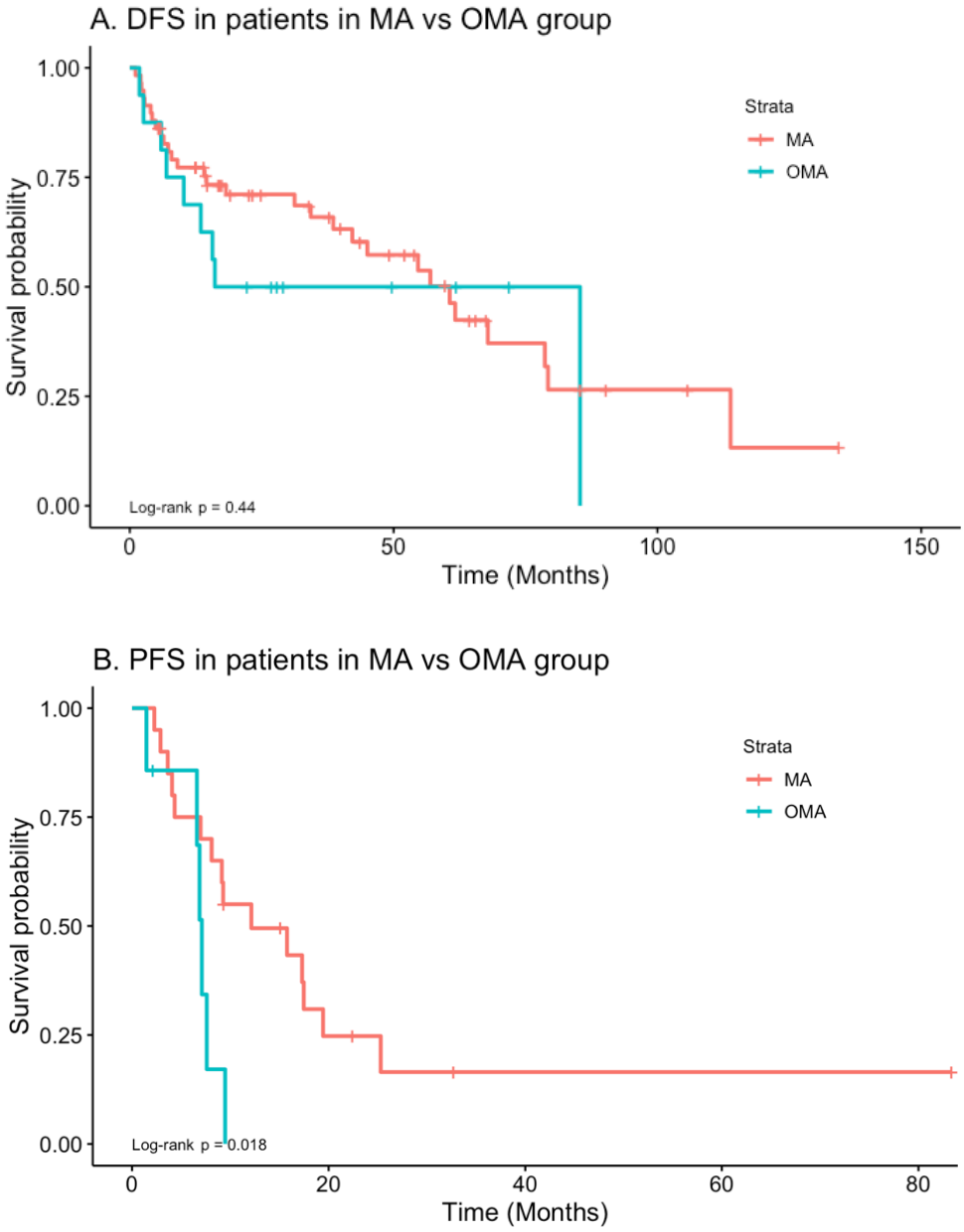
	MA (n=78)	OMA (n=23)	SMD
Length of Hospital Stay - Days (mean (SD))	15.70 (32.63)	14.09 (14.29)	0.064
Resection (%)			0.340
R0/R1	52 (38.2)	13 (23.1)	
R2	3 (5.5)	0 (0.0)	
Splenectomy (%)	9 (15.3)	1 (6.2)	0.294
Nephrectomy (%)	28 (47.5)	4 (25.0)	0.481
Distal Pancreatectomy (%)	4 (6.8)	1 (6.2)	0.021
Small Bowel Resection (%)	5 (8.5)	2 (12.5)	0.132
Right Colectomy (%)	5 (8.5)	1 (6.2)	0.085
Left Colectomy (%)	7 (11.9)	3 (18.8)	0.192
Sigmoid Resection (%)	5 (8.5)	4 (25.0)	0.454
Anterior Resection/Abdominoperineal Resection (%)	2 (3.4)	1 (6.2)	0.134
Diaphragm Resection (%)	3 (5.1)	1 (6.2)	0.05
Multi-Visceral Resection (%)	30 (50.8)	7 (43.8)	0.143
Creation of Loop Ileostomy (%)	1 (1.7)	0 (0.0)	0.186
Creation of End Colostomy (%)	2 (3.4)	1 (6.2)	0.134
Recurrence (%)	29 (37.2)	9 (39.1)	0.04
Local Recurrence (%)	14 (18.2)	5 (21.7)	0.089
Distant Recurrence (%)	16 (21.1)	4 (17.4)	0.093
DFS - Months (mean (SD))	35.80 (31.70)	27.99 (25.76)	0.270
PFS- Months (mean (SD))	16.04 (17.84)	5.89 (2.95)	0.794
OS- Months (mean (SD))	44.54 (39.57)	30.22 (25.47)	0.430

Table 4: Univariate and Multivariable Cox Regression Analysis

	Univariate Analysis HR (95% CI)	P-Value	Multivariable Analysis HR (95% CI)	P-Value
Disease-Free Survival (n=71, events: 35)				
OMA	1.34 (0.63-2.85)	0.443	1.36 (0.62-2.98)	0.437
Age (≤60)	1.10 (0.57-2.13)	0.767	0.98 (0.49-1.94)	0.944
Histologic Subtype (Ref: WDLPS)				
DDLPS	2.66 (0.73-9.66)	0.137	2.54 (0.69-9.28)	0.160
LMS	3.045 (0.87-10.69)	0.082	2.83 (0.78-10.26)	0.113
Other	8.93 (2.26-35.36)	**0.002**	8.95 (2.26-35.53)	**0.002**
Progression-Free Survival (n=27, events:21)				
OMA	3.39 (1.17-9.84)	**0.025**	3.50 (1.14-10.75)	**0.029**
Age (≤60)	1.20 (0.46-3.16)	0.706	1.86 (0.65-5.29)	0.244
Histologic Subtype (Ref: WDLPS)				
DDLPS	6.84 (1.21-38.77)	**0.030**	7.27 (1.18-44.68)	**0.032**
LMS	2.56 (0.49-13.26)	0.264	2.24 (0.43-11.75)	0.339
Other	3.25 (0.68-15.54)	0.140	3.58 (0.73-17.47)	0.115
Overall Survival (n=98, events:41)				
OMA	1.89 (0.96-3.73)	0.067	2.10 (1.05-4.23)	**0.037**
Age (≤60)	1.10 (0.57-2.13)	0.767	0.68 (0.35-1.30)	0.239
Histologic Subtype (Ref: WDLPS)				
DDLPS	1.82 (0.58-5.69)	0.301	1.59 (0.50-5.02)	0.429
LMS	1.36 (0.41-4.52)	0.618	1.34 (0.40-4.53)	0.638
Other	4.17 (1.38-12.6)	**0.011**	4.18 (1.38-12.65)	**0.011**

OMA: Outside of Census Metropolitan Area; WDLPS: Well-Differentiated Liposarcoma; DDLPS: Dedifferentiated Liposarcoma; LMS: Leiomyosarcoma; MVR: Multi-Visceral Resection

Figure 1: Kaplan-Meier Survival Curves for patients in the MA & OMA groups



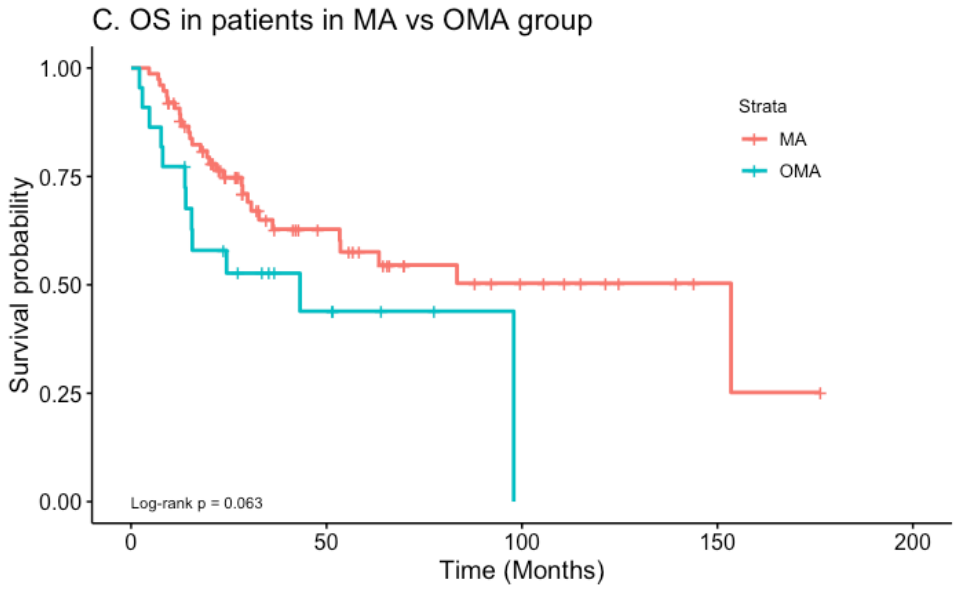


Figure 1: Kaplan-Meier survival curves comparing patients in MA and OMA group for DFS, PFS, and OS. (MA: Metropolitan area; OMA: Outside of Census Metropolitan Area, DFS: Disease-Free Survival, PFS: Progression-Free Survival, OS: Overall Survival)

Chapter 4 – DISCUSSION

4.1 General Findings

This thesis investigated the association between living within the same census metropolitan area as a sarcoma referral center and oncologic outcomes in patients treated for RPS. Evidence supports distance decay for several malignancies, including melanoma, rectal, testicular, breast, and cervical cancer[48,70,71].

The distance decay effect has been demonstrated in breast cancer, where women living in rural locations were less likely to receive timely mammography when compared to women living in urban settings[72,73]. When looking at all cancer mortality and access to radiotherapy in Canada, Chan et al found an association between decreased access to radiotherapy (via increased distance) and poorer cancer outcomes, particularly in lung and colorectal cancer[68]. In extremity sarcoma, Moten et al demonstrated that patients who traveled at least 15 miles had larger tumors (median size, 78 versus 70 mm; $P < 0.001$), higher odds of stage II compared to stage I disease (OR, 1.14; 95% CI, 1.04-1.24), longer median time to initiation of treatment or requiring more extensive surgery[74].

While these studies have attempted to identify the presence of a distance decay relationship, no studies have looked at distance decay relationships in RPS or the impact of distance on oncologic outcomes. In this thesis, we did observe an association between living outside of a sarcoma referral center's census metropolitan area and worsening oncologic outcomes, and is an independent predictor of worsening PFS and OS, after adjusting for age and histologic subtype.

However, is it distance per se that can explain the worsening oncologic outcomes observed in our study or is there a confounder related to the study that may also be able to explain these findings? Moreover, are certain aspects of treatment for a patient with RPS disproportionately affected for patients living farther away?

This thesis provides preliminary evidence to support the idea of distance decay in RPS and adds to the body of evidence that suggest this effect exists in other sarcomas (such as STS of the extremity[74]) as well as other malignancies. Moreover, this thesis identified significant delays in aspects of a patient's care, such as in receipt of neoadjuvant radiation therapy as well as undergoing percutaneous biopsy for tissue diagnosis of retroperitoneal masses.

4.2 Study Design

The study design and its limitations were addressed in the main manuscript presented in chapter 3, however, a more thorough discussion of the study design will be presented in this section.

The main study presented in this thesis was a retrospective single centre observational (cohort) study. The nature of a retrospective study is worthy of discussing. This was a study question that was developed a priori to data collection and included patients from 2008-2019. The research question and plan for statistical analysis of this study were also determined a priori to data collection, reducing the risk for hypothesizing after results are known (HARK). HARKing involves presenting a post hoc hypothesis as one that was developed a priori, where multiple hypotheses are tested in single datasets until statistical significance is achieved in a post-hoc analysis setting[75]. This can become problematic in epidemiology as multiple testing occurs when

multiple hypotheses are tested simultaneously. Due to chance and type 1 error, the more inferences tested, the higher the likelihood of finding a statistically significant result.

Despite the objective of the study being determined before data collection, the data collected is from patients who have already received their treatment and oncologic outcomes for most of these patients have already been determined. This means that some information of interest may not have been collected or available which can limit the precision of the study. As such, retrospective data collection is considered an inferior level of evidence compared to prospective studies where patients are recruited and there is more flexibility in information which can be gathered at the time.

One of the big limitations of collecting data retrospectively is recall bias, a systematic error where patients are asked to remember details from the past which may not be accurate or correct and lead to misclassification. In this study, outcomes were ascertained using patient records and information was collected via chart review for baseline information, pathology reports for histologic subtype, dates and reports of imaging for recurrence, progression or initial presence of the RPS. Death was recorded via the electronic medical record or publicly available obituaries. These sources would be considered objective findings which are traceable and not reliant on patient memory, therefore minimizing the risk of recall bias.

As this was an observational study for an uncommon disease, these limitations should be discussed as well. Given that there was no randomization from this study to ensure that the comparison groups are balanced to replicate (or come close to) the counterfactual model, and patients were recruited based on receiving treatment at a specific sarcoma referral centre, the presence of confounders and selection bias is a concern that must be acknowledged. Moreover,

as we compared patients who lived within and outside a specific census metropolitan area, since one area would be expected to be more populated (the patients who lived within the census metropolitan area), we expected the number of patients in each group to be different. In fact, in our cohort, 78 patients were included in the MA group and 23 patients were included in the OMA group. A priori sample size or power calculations were not performed as this was a retrospective cohort study within a defined time period and no possibility to include additional patients to improve power.

Another concern with patient selection is that there are several major sarcoma referral centres in Quebec, for which the referral pattern of each centre is unknown. We initially attempted to adjust for this this by using provincial health data (using the Régie de l'assurance maladie du Québec (RAMQ) administrative data), however the names of hospitals patients were treated at were redacted for confidentiality and therefore referral patterns could not be deciphered via this method. As such, this remains a concern for selection bias in this study. Within the 101 included patients, only 4 were lost to follow up. This low number is partially due to access to provincial wide imaging software where CT scans and reports are available from many hospitals in Quebec.

Since the study presented in this thesis was a retrospective cohort study, our sample size was limited to patients being treated for an uncommon illness at a single health centre. The data available in these patient records were not necessarily done so to evaluate oncologic outcomes for RPS. In addition, the McGill University Health Centre did not become a sarcoma referral centre until 2015, therefore the referral patterns from 2008-2015 may be different from 2015-2019. Although the official “referral centre” designation was not adopted , evidence for

improved outcomes with centralized RPS care began as early as 2004[76] and therefore referral patterns would likely be comparable even before this designation. In addition, when comparing oncologic outcomes of our cohort recruited before and after 2015, there are no statistically significant differences between groups.

Disease-free survival did not have a statistically significant effect in the univariate and multivariable analysis. This may in part be due to patterns of recurrence by histologic subtype. For example, Liposarcoma and leiomyosarcoma are associated with late recurrence and disease specific death (as long as 15 years from diagnosis). For subtypes such as solitary fibrous tumor, early distant recurrence was common (36% at 5 years) rather than local recurrence which was less common[50,51]. As liposarcoma and leiomyosarcoma account for the majority of subtypes in our sample, with late recurrence, it may be difficult to demonstrate statistically significant disease-free survival given this.

Given the limited sample size and the long disease-free interval in some subtypes of RPS, this may also introduce type II error. Post-hoc power calculations yield a power of 0.037 for DFS (35 recurrences in 71 patients, adjusted HR 1.36 for OMA), which we recognize is concerning for Type II error. Although it can be difficult to demonstrate statistically significant differences in oncologic outcomes for RPS, we were able to show statistically significant differences in both PFS and OS in our study. While type 1 error is important to consider, particularly for OS where the univariate analysis was not statistically significant for OMA, only two variables were adjusted for (with the lowest number of events in PFS – 21 events), minimizing the risk for overfitting in multiple regression.

Distance decay is a novel concept in sarcoma in general, but particularly in RPS where no published data is available which has investigated this effect. Given the small sample size and the retrospective nature of this study, this study was designed as a hypothesis generating study which will need to be reproduced in larger cohorts and involve multiple centres across the country, continent, or globe, given the rarity of this illness. Furthermore, before resources can be allocated in trying to counter the effects of distance decay in RPS care, once larger studies have confirmed that this effect exists in RPS, further research will be needed to investigate what factors associated with distance can be targeted to reduce the inequality observed in our study. There has been a shift to centralized care observed over the years for many complex diseases requiring the expertise of multidisciplinary teams[41-47]. Centralization of care improves health outcomes for some diseases, however, as access to tertiary or quaternary care becomes necessary to facilitate management of a centralized illness, travel times may understandably increase. As such, access to healthcare services, particularly by patients living in rural areas, may worsen over time[77,78]. This may create larger inequalities for patients living in rural areas or further away from specialized referral centres. For this reason, we thought this was an important concept to investigate for RPS.

However, the ideal study design to answer our research question would be a multicentre prospective cohort study to assess exposure of distance to care. Every aspect of care for RPS, including but not limited to time of symptom onset to seeking primary care/emergency room services, timing to imaging, biopsy, visit with consultants, etc. should be obtained to better understand which aspects of care are most affected by distance. Given that distance or rurality cannot be randomized, the gold standard study design of a randomized control trial would not

be possible in this context. However, with more information on aspects of care that are delayed, such as initiation of neoadjuvant radiation therapy as seen in our cohort of patients in the OMA group, there would be enough clinical equipoise to design randomized control trials around this topic. For example, neoadjuvant radiation for RPS is usually a long course of radiation which occurs over an extended period of time (usually 50.4 Gy of radiation given over 28 days)[55], it may be more difficult to schedule for patients living further away who would need to find lodging for this time period. A trial where temporary housing close to the hospital arranged by the radiation oncology team may be considered, where patients can be randomized to receiving temporary housing and standard of care (where housing is not offered) and delays to initiation of radiation therapy or oncologic outcomes can be measured.

4.3 Statistical Analysis

The statistical analysis and its limitations were addressed briefly in the main manuscript presented in chapter 3, however, a more thorough discussion of the analysis will be presented in this section. In this thesis, the study presented assessed oncologic outcomes from RPS, comparing DFS, PFS and OS between patients in the MA and OMA group. In addition to univariate and multivariable cox regression analysis, Kaplan-Meier survival curves to estimate the cumulative probability of survival over time.

The outcomes of interest were DFS, PFS, and OS. DFS is defined as the time from curative treatment to evidence of recurrence of the tumor[79]. In our cohort, this was calculated by date of surgery for patients who underwent R0 or R1 resection (both are considered complete resection for RPS, whereas R2 resection indicates that the tumor was incompletely resected at a

macroscopic level) and the date of radiologic recurrence of RPS, usually found with surveillance CT scans which are usually performed every 3-6 months for the first 2 years, every 6 months for the following 2 years (between 2-4 years after resection), and then annually after that[80]. DFS is sometimes divided into local recurrence and distant metastases, however given the small sample size of our cohort, both recurrence patterns were combined for our analysis.

PFS is defined as the length of time from where a patient is diagnosed with unresectable RPS, to the time where there is evidence of increasing disease burden[81]. For RPS, this includes the time where a patient is diagnosed, is deemed not to be a surgical candidate (advanced disease where surgery cannot remove all of the cancer or patient is too frail for surgery) and is offered palliative radiation therapy, chemotherapy, or no treatment, to the time where radiologic evidence of disease progression (tumor size increases or metastatic disease develops). In our cohort, this was calculated by the first radiologic evidence of disease to radiologic evidence (usually CT scan) demonstrating disease progression.

OS is defined as the time from diagnosis of disease to date of death. For our study, this was calculated by looking at the first date of radiologic evidence of disease to the date of the patient's death. OS included all patients treated for RPS in the study, which included patients who underwent surgery for curative intent (R0/R1 resection), R2 resection, and patients who underwent palliative treatment for unresectable disease or no treatment. DFS and PFS are sometimes used as a surrogate marker for OS, particularly in diseases with long survival periods[82,83].

In table 1 of our manuscript where we compared baseline characteristics between MA and OMA group, we used the standardized mean difference (SMD) to compare differences

between groups. SMD was initially developed for comparison of means of continuous variables between groups. However, given that many covariates are dichotomous in clinical research, it is also used in this context[84]. For comparing differences between groups, we preferred using SMD over the conventional p-value. P-value is set arbitrarily (usually at less than 0.05) and is essentially a measure of an association between groups due to chance. It does not provide any information on effect measure. SMD is a ratio calculated calculating the difference in means between groups and then dividing this by the standard deviation of the variable among the cohort groups. If SMD were 0, this would suggest a perfect balance between groups. If SMD were 1, this would suggest complete or infinite imbalance. In general, a SMD of 10% (0.1) or less indicated a negligible different between groups[85,86]. Unlike the p-value, the SMD provides an effect measure to suggest a magnitude of difference of the baseline characteristics between groups.

The Cox regression model follows a semi-parametric distribution. It is commonly used to study effects of variables on time. For our study, the "time" we were interested in was the time of patients without evidence of RPS following surgery (DFS), time until RPS disease burden increases (PFS), and time patients are alive from diagnosis of illness (OS). In a Cox proportional hazards (PH) regression model, the effect measure of interest is the hazard rate, which is the rate of experiencing an event (i.e., recurrence (DFS), progression (PFS) and death (OS) as events). In Cox PH, the model does not use an intercept, which means that a baseline hazard for an event does not need to be known. This model can then be used to compare relative hazard rates between groups and provide a hazard ratio rather than absolute rates.

Three important assumptions must be met for proper use of Cox PH regression models. These assumptions are: 1) independent time to events between participants, 2) a hazard ratio

that is constant over time, 3) multiplicative relationship between the variables of interest and the event. In our study, we believe that all assumptions were met in the analysis performed. The hazard rates would differ by histologic subtype of RPS, however subtypes were present in both groups and was a variable adjusted for in our multivariate model. In addition, in our KM curves, most of our events occurred early for recurrence, however this was constant between both groups in our curves.

Since our oncologic outcomes of interest had a time component, a Cox PH model was felt to be the most appropriate statistical test for our study. As logistic regression largely ignores the time component that was important in our study and compares the proportion of events between groups, we felt this would not be an appropriate statistical test for our study. Moreover, in oncology research, as time to event data is very relevant, censoring becomes an important consideration as patients are lost to follow-up or the study period ends when the event does not occur to a patient. As Cox PH takes censoring into consideration, we felt it was an appropriate model to use in our study.

In our study, hazard ratio for DFS was not found to be statistically significant, while hazard ratios for OS was statistically significantly higher in the multivariate model. As time to event for OS is often longer than for DFS as dying from an illness would involve relapsing or recurrence from the illness of interest, this result merits further discussion. Our analysis demonstrated a strong signal suggested by statistical significance in both the univariable and multivariate model in PFS. Since OS included all patients from the study (both patients who underwent surgery and included in the DFS analysis and those who did not undergo surgery and underwent palliative treatment or no treatment in the PFS group), we believe the findings of DFS in this thesis to be a

result of type II error. As more patients in the OMA group presented with larger tumor size and with metastatic disease, and with DFS having a signal towards higher DFS in the MA group, we believe that a larger sample size of patients would likely show a similar relationship for DFS as it did for OS.

In this study, we chose to adjust for age and histologic subtype. Given the low sample size and number of events between groups, we were somewhat limited in the number of covariates we were able to adjust for. In our study, the covariates in our model were chosen based on a priori knowledge of risk factors for disease recurrence/progression/survival in RPS. Histologic subtype is an important covariate to consider given the strong evidence in the literature that histologic subtypes in RPS can have extreme variation in rate of recurrence, patterns of metastases and ultimately overall survival[26,87-89].

Age was another covariate we used in our model and is also commonly used in oncologic research as a marker of overall health. There are often other measures of overall comorbidity in medical research, such as the Charlson comorbidity index (CCI)[90]. However, as all patients in this study have a solid tumor malignancy, and this being a variable in their calculation, we were unsure of its utilization as patient selection would have an inflated CCI score. We used an "adjusted CCI" where scores were calculated and the solid cancer option was left out and was included in our manuscript, however we were unsure what the utility of this adjusted score would be and decided not to include it in our final model. In preliminary analyses, using our "adjusted CCI" did not change the overall significance of our results in DFS, PFS, and OS.

Lastly, completeness of resection (R0/R1/R2 resection) is another important marker for recurrence and overall survival in RPS and oncology in general. While the goal of RPS surgery is

complete resection, given the large size of tumors in RPS, it is very difficult to obtain accurate pathologic assessment of all margins on the resected tumor. As such, both negative margins (R0) and positive microscopic margins (R1) are considered "complete resection" in RPS[56]. In our study, we had very few R2 resections (3 in total) and therefore did not think this would be an informative covariate in our model.

Chapter 5 – CONCLUSION

This thesis was the first study to look at distance from a sarcoma referral centre or urban-rural differences in oncologic outcomes in RPS. In the manuscript associated with this thesis, we were able to provide preliminary evidence that patients living outside the census metropolitan area of a sarcoma referral centre were assessed with more advanced disease at presentation and had notable worsening in PFS and OS. These interesting findings may suggest that mechanisms exist in patients living further away from a sarcoma referral centre, or patients living in rural areas which leads to worsening oncologic outcomes in RPS.

These preliminary findings should drive future research into specific mechanisms in distance which contribute to these important findings and to develop solutions or research potential strategies which will mitigate this inequality.

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