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Diogo Esteves Fernandes

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Diogo Esteves Fernandes

Aluno do 6° ano profissionalizante de Mestrado Integrado em Medicina

N° de aluno: 201305490

Afiliação: Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço: Rua de Jorge Viterbo Ferreira nº228, 4050-313 Porto

Endereço eletrónico: diogoefernandes@gmail.com

Orientador: Pedro Filipe Ferreira Cardoso

Assistente Hospitalar Graduado do Serviço de Ortopedia – Centro Hospitalar do Porto

Afiliação: Professor Auxiliar de Ortopedia do ICBAS

Endereço: pffcardoso@gmail.com

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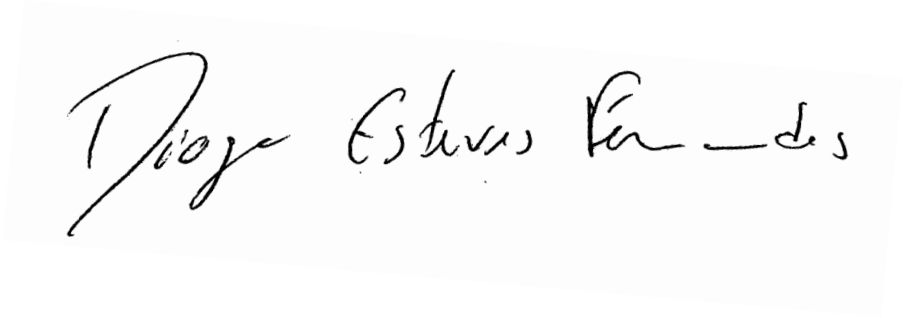

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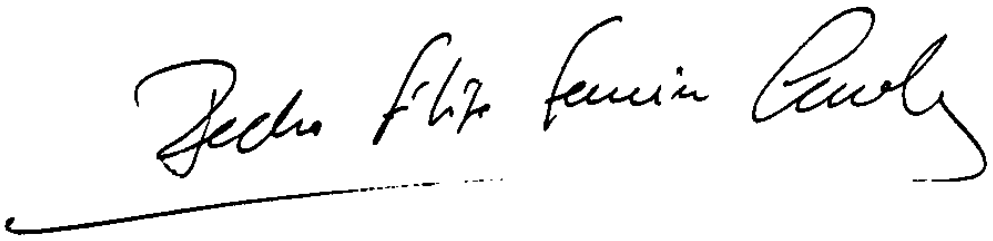

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Resumo

Os Tumores Malignos das Bainhas Nervosas Periféricas são sarcomas de tecidos moles muito raros que apresentam uma diferenciação celular em células presentes nas bainhas nervosas. Aproximadamente 50% dos casos da doença ocorrem em doentes com história de neurofibromatose tipo 1, uma doença hereditária que predispões os doentes a desenvolver múltiplos neurofibromas que podem eventualmente degenerar em tumores malignos das bainhas nervosas periféricas, especialmente em doentes que apresentam neurofibromas plexiformes. Estes são tipicamente tumores que apresentam alto grau de diferenciação, comportando-se de uma forma agressiva com elevadas taxas de metastização e de recorrência pós-cirúrgica. Os autores pretendem estudar a doença nos seus aspetos diagnósticos e terapêuticos assim como contribuir para uma melhor compreensão dos fatores que podem afetar o prognóstico dos doentes.

O estudo incluiu um total de 12 doentes que foram diagnosticados e tratados num centro de referência de sarcomas músculo-esqueléticos nos últimos 17 anos. Foram recolhidos dados demográficos, clínicos, imagiológicos e patológicos, assim como dados relativos à sobrevida livre de doença, ocorrência de metastização à distância e sobrevida total. Os resultados mostraram elevadas taxas de recorrência e de metastização com valores de 62,5% e 66,7% respetivamente e a sobrevida aos 5 anos foi de 25%.

O prognóstico destes doentes é muito pobre daí que seja importante que estes doentes sejam abordados por uma equipa multidisciplinar de forma a serem diagnosticados e tratados o mais prontamente possível. Após o tratamento deve ser realizado um seguimento aos doentes uma vez que estes tumores apresentam elevadas taxa de recorrência. Ainda não existe consenso no que diz respeito ao prognóstico dos doentes com e sem neurofibromatose tipo 1, no entanto, a comunidade científica reconhece que, na presença desta doença, o risco de desenvolver estes tumores malignos está aumentado. É pois extremamente importante que estes doentes sejam avaliados regularmente para pesquisa de neurofibromas com caraterísticas atípicas de forma a prevenir a degeneração dos neurofibromas em lesões malignas.

Palavras chave: Tumores Malignos das Bainhas Nervosas Periféricas, Neurofibromatose Tipo 1, Neurofibroma, Sarcomas de Tecidos Moles.

Abstract

Malignant Peripheral Nerve Sheath Tumors (MPNST) are a very rare soft tissue sarcomas that show differentiation toward cells of the nerve sheath. Approximately 50% of the cases of the disease occur in patients with history of neurofibromatosis type 1 (NF1), a hereditary condition that predisposes patients to develop multiple neurofibromas that can eventually degenerate into MPNST, especially in patients with plexiform neurofibromas. MPNST are usually high-grade tumors that behave aggressively and show elevated capability of metastize and high incidence of recurrence post-surgery. Authors intend to study this disease in its diagnostic and therapeutic aspects and hope to contribute to a better understanding of factors that may influence outcomes of patients.

This study included a total of 12 patients who were treated and diagnosed with MPNST by pathology in a reference center of musculoskeletal sarcomas over the last 17 years. Data covered the demographical, clinical, imaging and pathological elements as well as disease-free survival, occurrence of distant metastases and overall survival. Results showed high recurrence and metastatic rates of 62,5% and 66,7% respectively and the 5-year survival was 25%.

Prognosis of patients with MPNST are typically very poor so it is important that patients can be approached by a multidisciplinary team in order to be precociously diagnosed and treated. A proper follow-up should be performed since these tumors have high recurrence rates. It is still unclear if patients with hereditary syndrome neurofibromatosis type 1 have worse prognosis than patients with sporadic MPNST, however what is acknowledged is that patients with NF1 have much higher risk of developing MPNST so it's important that these patients can be routinely scanned for neurofibromas with atypical features so we can prevent the degeneration of neurofibromas into MPNST.

Keywords: Malignant Peripheral Nerve Sheath Tumors, Neurofibromatosis type 1, Neurofibroma, Soft Tissue Sarcomas.

Abbreviations List

MPNST – Malignant Peripheral Nerve Sheath Tumors

NF1 – Neurofibromatosis type 1

GTPase – Guanosine Triphosphate hydrolase

MAPK – Mitogen Activated Protein Kinases

CT – Computed Tomography

MRI – Magnetic Resonance Imaging

PET – Positron Emission Tomography

FDG – Fluorodeoxyglucose F18

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Introduction

Malignant peripheral nerve sheath tumors (MPNST) are very rare and aggressive soft tissue sarcomas arising from cells of the peripheral nerve sheath or cells that undergo into differentiation towards those cells. These tumors were frequently referred as malignant schwannoma or neurofibrosarcoma, nevertheless the most accurate term to address these tumors is MPNST since the histopathological appearance of these tumors can include a lot of different cellular types present in the nerve sheath, cells like Schwann cells, perineural fibroblasts, or fibroblasts.[1] These tumors are extremely rare being merely the sixth most common sarcoma, corresponding to approximately 5% to 10% of all soft tissue sarcomas. Among the general population the incidence of these tumors is very low with an expected value of 1/1,000,000 per year.[2]

The literature describes two major risk factors to the emergence of these tumors: hereditary syndrome neurofibromatosis type 1 (NF1) and previous radiation exposure. Approximately 50% of patients with MPNST are diagnosed in patients with NF1, a hereditary condition in which occurs a mutation affecting the gene neurofibromin 1, a gene located on chromosome 17 in humans, responsible for the codification of neurofibromin, a GTPase-activating protein that negatively regulates the RAS/MAPK pathway activity. The misfunction of the protein neurofibromin leads to a dysregulation of intracellular pathways that modulates the proliferation, growth, and apoptosis of the cells culminating in malignancy transformation. Patients with NF1 tend to present a lifetime risk of developing a MPNST as high as 13% especially those with plexiform neurofibromas associated to a higher risk of malignant transformation. The incidence among NF1 patients is 1/3,500.[3]

The other main risk to the arising of MPNST is previous radiation exposure. Several reports confirmed the appearance of these tumors at sites previously irradiated [4] and it's been shown that irradiation of peripheral nerves produces marked proliferation of Schwann cells and endoneural fibroblasts as well as nuclear and chromosomal abnormalities [5], up to 10% of MPNST are related to previous sites of irradiation.[1] The remainder affect individuals without a known genetic predisposition.

Patients with MPNST describe a rapidly enlarging mass within months and symptoms like pain and neuropathic symptoms such as paresthesia, motor weakness or radicular pain and sometimes, in more advanced cases, ulcerative epidermal lesions.[6] The typical age of presentation is 20-50 years, although they can be diagnosed in children as well, especially in

children with NF1. The tumor arises in a variety of body segments yet, the most affected segments are the extremities, followed by the trunk and the head and neck areas.[7] The gold standard diagnostic method to MPNST is the histopathology but, prior to the biopsy, a radiological examination should be performed including a CT scan and a MRI (Figure 1) of the affected area and, in some cases, the patient can benefit from a FDG-PET as MPNST can present an increased FDG uptake.[8]

Histopathological samples show spindle cells with a fascicular growth pattern. A branching haemangiopericytoma-like vascular pattern can be present, as well as hypercellular and hypocellular areas. Cells can have a whirling or rarely palisading growth pattern and geographic areas of necrosis. The neoplastic cells are mitotically active, spindle-or serpentine-shaped with hyperchromatic nuclei and pale cytoplasm. Heterologous elements, such as skeletal-muscle, bone, cartilage, and blood vessels, are present in approximately 15% of the tumors.[9]

Treatment should take into consideration factors like staging, capability of performing a wide excision, age of the patient, presence of NF1 and other factors that could affect the prognosis. MNST have higher recurrence rates compared to other soft tissue sarcomas[10] and, if localized, demands wide excision (Figure 2) and adjuvant radiotherapy in order to avoid recurrence. In cases of advanced or metastatic MPNST, outcomes are generally poor and the treatment of choice is often chemotherapy being the combination of doxoruibicin and ifosfamide the best option since the combination of these chemotherapeutic agents have shown the best results in unselected soft tissue sarcomas. [11]

Most of MPNST diagnosed are high-grade sarcomas with very poor prognosis. Patients with unresectable diseases or with metastasis at presentation undergo through chemotherapy but only 20-50% of patients respond to this treatment. [12] Patients with resectable tumors are submitted to surgery and radiotherapy however the rate of local recurrence is estimated to be 40-65% and up to 30% to 60% of patients develop metastasis (about 65% to the lungs).[13-14] In high-grade MPNST, overall 5-year survival rate is about to 20% to 50% and mortality up to 75%.[15]

Authors present a series of cases of MPNST diagnosed and treated at a reference center of musculoskeletal sarcomas. The goal is to study a rare disease in its diagnostic, and especially, therapeutic aspects since wide resection of these usually large tumors represents a huge technical challenge to surgeons and result in elevated morbidity to patients. There will be focused the following aspects: location, surgical margins, recurrence and metastasis.

Materials and Methods

Authors analyze a series of 12 patients with MPNST treated between 2003 and 2020 in one single institution. Collection of data was performed by consulting electronic and physical files containing: clinical notes, radiographic images, pathological reports and operative notes of patients. Data covered the demographical, clinical, imaging and pathological elements as well as disease-free survival, occurrence of distant metastases and overall survival.

Table I provides patient's demographical data, location of the tumor, evolution time of the mass and symptoms, type of biopsy performed, history of NF1 as a risk factor to MPNST, staging, treatment, and surgical margins managed.

The gender ratio is 1:1 (6 male to 6 female) and the mean age was 56.3 years (range 23-83). The anatomical distribution of the tumors was: 5 at the lower extremity, 4 at the upper extremity, 2 at the trunk and 1 at the head (Figure 3). The preoperative syndrome duration (PSD) was defined as the time between the beginning of the symptoms till the beginning of treatment, and it was 5.25 months ranged from 2 to 15 months. In this series, 4 of 12 patients had history of NF1 and none of them had history of radiotherapy. Biopsies were incisional (n=5), excisional (n=3), and true-cut (n=4). At the time of presentation all patients had high grade tumors and only 3 of them showed distant metastasis all in the lungs. Patients were treated taking in to account the possibility of tumor resection and the presence or absence of metastasis at presentation: 5 patients underwent through surgery and adjuvant radiotherapy; 2 patients had their tumors resected only; 3 patients were treated with palliative radiotherapy; and 1 patient was treated with surgery and palliative chemotherapy. The surgical margins applied in the patients that were operated were R0 (n=7), R1 (n=1), and R2 (n=1).

Results

The average follow-up of the patients was 35,9 months (ranging 6-121 months). Table II presents data concerning the emergence of local recurrence and metastasis, disease-free survival, metastasis-free survival, overall survival and the outcome of the patients.

Out of the 12 patients studied 5 experienced local recurrence and 3 were not operated due to impossibility of resection of the tumor. One patient underwent amputation. The recurrence rate was 62,5% (5/8).

Concerning to secondary lesions 8 patients had metastasis corresponding to 66,7% being: 3 of at the time of the diagnosis, all in the lung. Of the remaining 5, 3 showed lung metastasis and 2 had metastasis in different locations.

The disease-free survival (DFS) corresponds to the period of time in between the surgery and the diagnose of local recurrence or metastasis. The average disease-free survival was 34,4 months (ranging 2-121 months) excluding patients that did not undergo through surgery. Metastasis-free survival corresponds to the period of time since the surgery to the diagnose of metastasis and the average duration was 37,7 months (ranging 7-121 months). This value excludes patients with metastasis at presentation.

A total of 9 patients died during follow-up corresponding to 75% of our patients, the average overall survival was 35,9 months (ranging 6-121 months) and the 5-year survival rate was 25%.

Discussion

MPNST are relatively rare and aggressive neoplasms of the soft tissues. Due to its rarity there have been limited number of studies about the disease. Despite the reduced numbers of cases, authors considered important to publish data about patients diagnosed and treated at our institution from the last 17 years with the expectation of contributing to a better understanding of the factors that directly affect the typically poor prognostic of patients with MPNST.

Local recurrence and distant metastatic disease are widely recognized as factors of poor prognosis for patients with MPNST and, in this regard, treatment and follow-up instituted aimed to reduce the occurrence of those complications. Local recurrence rates are higher in patients with MPNST than in patients with other soft tissue sarcomas [10], with reported recurrence rates up to 65% [13-14], therefore, the preferred treatment is the excision of the mass with wide margins (R0) followed by adjuvant radiotherapy. Our case analysis showed that 62,5% of the patients that underwent through surgery experienced local recurrence. In terms of diagnose of distant metastasis, our study revealed that 66,7% had metastases and those patients can be divided into 2 groups: patients with metastases at presentation and after local recurrence. This shows us the importance of a close follow-up of patients after treatment aiming to detect and treat possible recurrences as early as possible.

Another factor that has been discussed in the prognosis of these patients is the presence or absence of the hereditary syndrome NF1. There's no agreement on how prognostic of patients with NF1 differ from patients with sporadic MPNST. Reports have shown that patients with NF1 are diagnosed with MPNST at younger ages [16] and the ones that report a poorer prognostic of patients with NF1 show that these patients tend to be diagnosed with MPNST at more advanced stages [17] and to present differences in the genetic profile of tumors arising in these 2 groups.[18]

Tumor resection method is also a universally recognized prognostic factor in these patients. Porter et al.[16] showed statistically significant differences in local recurrence rates on patients that had surgery with wide margins vs patients in whom adequate margins weren't achieved (6% versus 30%). In our study 42% of patients operated with wide margins had local recurrence of their tumor. Other 2 factors that should be taken into consideration are: body segment affected by the MPNST and the volume of the lesion. These factors are important because they have an impact in the capability of the surgeon excise the lesion with clean margins. In our cases only 2 patients had not their tumors removed with wide margins, a patient with a MPNST at the left jugular foramen due to impossibility of getting better margins at that location, and a patient with a metastasized tumor at presentation and both of them presented later local recurrence and metastasis.

These patients presented poor outcomes with a mortality rate of 75% and a 5-year overall survival of 25%, a value lower than the value reported of 30-50%.[19]

Conclusion

MPNST are rare and aggressive soft tissue sarcomas whose presentation is often through rapidly enlarging masses typically within months. The approach of this patients should be performed by a multidisciplinary team for a more appropriate and faster diagnose and treatment so it can be possibly to improve the prognostic of these patients. It's important to have a close surveillance of patients with NF1 mainly the ones with plexiform neurofibromas as these neurofibromas have higher risk of malignization into MPNST. The treatment of choice should always be the surgery and if possible with wide margins. Adjuvant radiotherapy should also be considered but in patients with NF1 the necessity of radiotherapy must really be weighted because the irradiation of neurofibromas is a risk factor to the emergence of a MPNST. After treatment a close follow-up should be performed in order to precociously detect recurrence of the lesion.

Appendix

Table I- Patient Information, Clinical Features, Management

Case	Gender	Age (years)	Tumor location	Biopsy	NF1	MAP	Surgical Margins	Treatment	PSD (months)
#1	F	78	right leg	Incisional	N	N	R0	S + aRt	15
#2	F	83	right leg	Incisional	N	Y	NO	pRt	4
#3	F	68	L5	Incisional	N	N	NO	pRt	6
#4	F	45	right halux	Incisional	N	N	R0	S	4
#5	F	60	left jugular foramen	Excisional	Y	N	R1	S + aRt	6
#6	M	78	left forearm	Excisional	N	N	R0	S	3
#7	M	82	lower back	Incisional	N	Y	NO	pRt	7
#8	M	39	left hip	True-cut	Y	N	R0	S + aRt	2
#9	M	46	right arm	True-cut	Y	Y	R2	S + pCt	4
#10	M	26	left forearm	True-cut	Y	N	R0	S + aRt	6
#11	M	23	3rd finger left hand	Excisional	N	N	R0	S	3
#12	F	48	left hip	True-cut	N	N	R0	S + aRt	3

NF1: neurofibromatosis type 1; MAP: metastasis at presentation; PSD: preoperative syndrome duration; S: surgery; aRT: adjuvant Radiotherapy; pRt: palliative Radiotherapy; pCT: palliative chemotherapy; NO: not operated.

Table II - Follow up and Outcome

Case	Recurrence	Metastasis	DFS (months)	MTX free survival (months)	Overall survival (months)	Outcome
#1	A	Y	18	18	28	Dead
#2	NO	Y*	-	-	24	Dead
#3	NO	N	-	14	14	Dead
#4	N	N	77	77	77	Alive
#5	Y	Y	48	60	77	Dead
#6	Y	Y	7	7	23	Dead
#7	NO	Y*	-	-	6	Dead
#8	Y	Y	2	7	8	Dead
#9	Y	Y*	4	-	11	Dead
#10	N	N	19	19	19	Alive
#11	N	N	121	121	121	Alive
#12	Y	Y	14	16	23	Dead

DFS: Disease free survival; Y: Metastasis at presentation; NO: not operated*

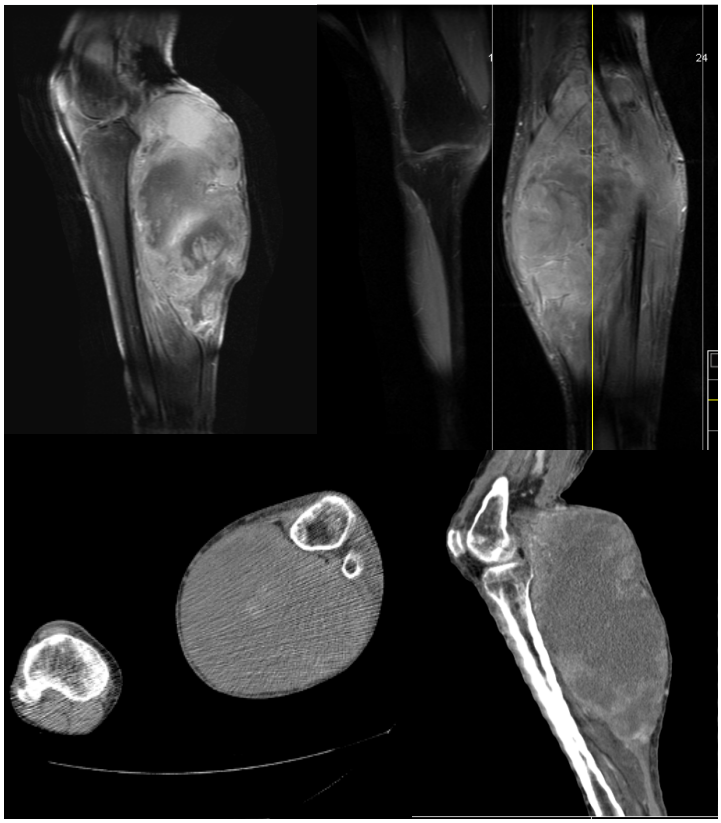

Figure 1 - Radiographic study of a MPNST in the posterior left leg

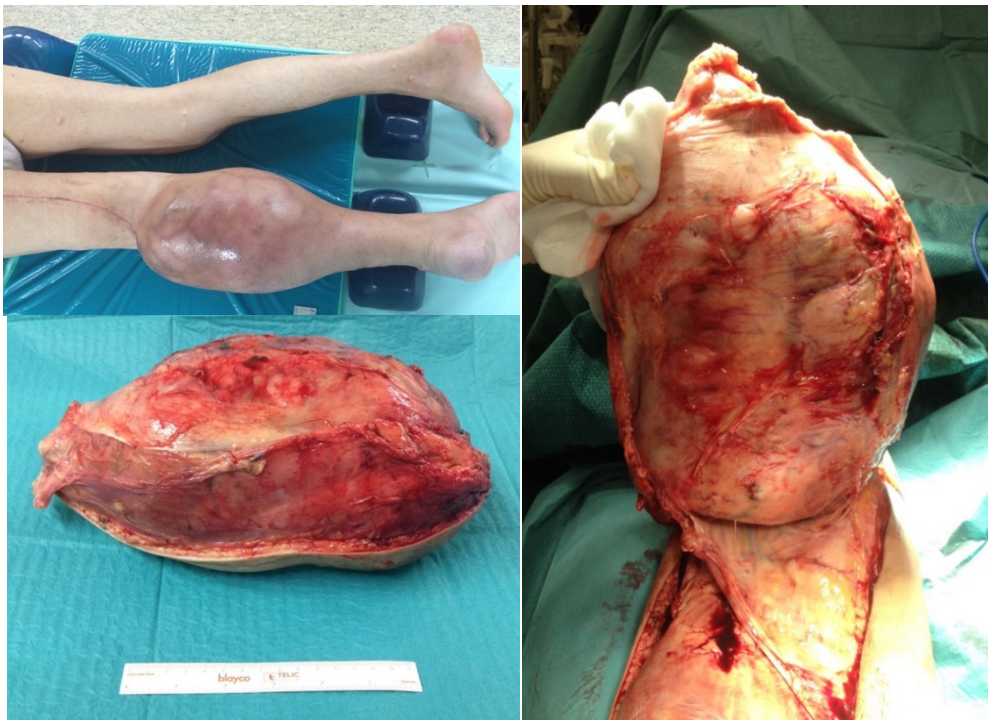

Figure 2 - Photographic documentation of the excision of a MPNST in the posterior left leg

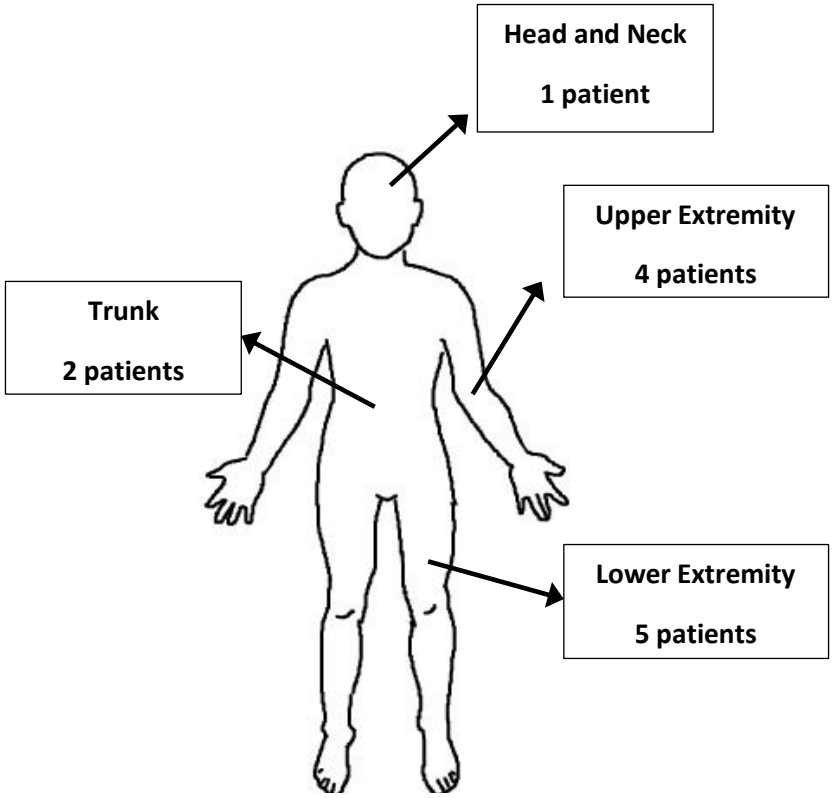

Figure 3 - Representation of the anatomical distribution of MPNST in patients

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