Lung metastases from Soft Tissue Sarcoma

Summary

Soft tissue sarcoma (STS) represents a heterogeneous group of malignant neoplasms developing in non-epithelial extraskeletal tissues. Therefore, they may grow in muscle, fat, fibrous tissues, nerves, blood vessels, or deep skin tissues. However, they arise more frequently in the extremities with the thigh being the most common site in the body, with 44% of all extremity STS.

Since their annual incidence rate is approximately 2 per 100.000, STS are considered rare cancers, representing 1% of adult malignancies and, based on current statistics provided by the Surveillance, Epidemiology, and End Results (SEER) program, the mean age at diagnosis is 58 while the mean age at death is 65.

Lung metastases (LM) are the most frequent consequence of STS. Approximately an average of 25% patients develops pulmonary metastases in the course of their disease and about 10% present synchronous metastases. The lungs are the most common site of synchronous and metachronous metastases, and in more than half of the patients with advanced STS the lung is the only site of recurrence. Pulmonary metastases may arise from any primary site, although there is evidence that they most frequently arise from extremities sarcoma. Nonetheless, while a lot of research has been focused on the primary tumor, less is known about the diagnosis and the treatment of LM are a challenge for clinicians, since LM represent an advanced stage of the disease and are the most frequent cause of death.

The main aim of this thesis was to get more insights into diagnosis, treatments, and prognostic factors of LM secondary to soft tissue sarcoma with a glance to future perspectives.

In the **Chapter 2** of this Thesis, we have dealt with the very challenging problem of identifying LM from STS. We have demonstrated that lung nodules > 5.6 mm, well-defined margin nodules, increased size from baseline CT, and a new onset nodule, increase the risk of malignancy up to 28 times when associated with synovial sarcoma histology. However, our data have highlighted that without the support of clinical data, many CT features lose their specificity.

In **Chapter 3,** we explored the disease-specific mortality instead of overall mortality after LMTS and, starting from this assumption, searching for adjusted- accurate mortality-preoperative predictors of MTS lung recurrence. We found that, concerning specific mortality, synovial sarcoma and myxofibrosarcoma showed the lowest survival increasing the risk of disease-specific death by 2.5 times.

In **Chapter 4** we reviewed the available literature and performed a metanalysis to evaluate stereotactic body radiotherapy (SBRT) for the treatment of STS. The message that emerged from this analysis was that, in the absence of a direct comparison, SBRT appears to be a reasonable alternative to mastectomy in selected patients with lung metastatic STS.

In **Chapter 5,** a literature review was performed to explore the survival rate and local control of patients with metastatic STS patients treated with SBRT and Radio-Frequency Ablation (RFA). SBRT is recommended in patients unsuitable for surgery, and in case of synchronous bilateral pulmonary metastases requiring surgical bilateral thoracic approaches that can be replaced by a hybrid approach surgery/SBRT.

Ablation is more successful in case of long disease-free interval between the primary tumor treatment and metastases' appearance (>36 months), oligometastatic disease (i.e., <3-5 metastases), disease involving only the lung (or a small number of extra-thoracic locations), small size nodules (up to 2-3 cm of larger diameter), lesions far away from large vessels.

In Chapter 6, we explored the survival benefit of adjuvant chemotherapy after the first lung metastasectomy in high-grade synovial sarcoma (HGSS) patients. HGSS was chosen because synovial sarcoma (SS) seems to be relatively chemosensitive among STS, and neoadjuvant treatments were proven to improve survival. Patients undergoing adjuvant chemotherapy after

LMS showed 5-year freedom from SS-specific mortality significantly lower than patients not treated. In addition, chemotherapy raised the risk of death by 2.5 times during the follow-up. This data must be read with great care since chemotherapy is often administered to patients with advanced disease and unsuitable for radical surgery. A strength of our research is that we managed to have well-balanced groups (chemotherapy/no chemotherapy) to reduce the brisk of bias.

In **Chapter 7,** we tested the feasibility and the performance of a machine learning (ML)-based model to predict recurrence of lung metastases after the first LMTS for STS.

We found a high-performance model which showed that age at the primary tumor diagnosis is the most crucial feature (100%) related to recurrence of LM after the first LMTS for STS.

In conclusion, a prompt detection of PN malignancy is crucial in these patients, considering the highly aggressive nature of STSs, the high risk of MTS outside the lungs, and the high success rate gained when metastases are localized only in the lungs.

This thesis wants to be a call for gathering data in disease-specific registries for further large studies that can help clinicians to deal with this aggressive disease and improve patient's survival and quality of life.