Osteosarcomas are rare with an estimated incidence of 5-6 cases per million population per year but still represent the most common primary malignant tumors of bone. They generally affect the metaphyses of long bones in children and adolescents and primarily originate within bone (intramedullary osteosarcomas) while only a minority develop on the bone surface (10%). Low-grade lesions are usually treated by surgery only but more than 90% of cases represent high grade tumors and follow an aggressive clinical course. Before the introduction of (neo-)adjuvant chemotherapy, more than 90% of those patients developed metastases despite immediate resection and only few patients survived. Consequently, osteosarcoma is regarded a systemic disease at the time of diagnosis. With current treatment protocols, however, long-term survival in up to 70% of patients can be achieved, especially in those patients that respond well to neoadjuvant chemotherapy. In fact, the histologic assessment of the response to therapy is still the gold standard in predicting the prognosis of osteosarcoma patients, a purely morphological method which aims to determine the percentage of vital tumor residues after cytotoxic therapy and which was introduced in the beginning of the 1980s. That such a rather "old-fashioned" technique is still in routine use is in line with the fact that the prognosis of osteosarcoma patients has not significantly improved in the last 30 years and still leaves a subset of patients without effective treatment options. One of the reasons for this dismal situation is the enormous genetic heterogeneity of osteosarcomas with not only a single signalling pathway affected but a multitude of genetic alterations hampering the identification of initiating genetic hits. In at least a subset of tumors, a single catastrophic event called chromothripsis seems to be one of the mechanisms causing genetic chaos and to correlate with an adverse outcome of patients. Another major problem in osteosarcoma research is the lack of sufficient tissue samples to conduct molecular analyses. Since patients are generally treated by neoadjuvant chemotherapy which (ideally) destroys or significantly alters the tumor tissue, only the initial biopsy, obtained for diagnostic purposes, is suitable for scientific analyses. However, this biopically acquired tissue is completely needed for rendering an adequate diagnosis (with major clinical impact) in most cases so only if tissue remains it can be used for scientific purposes. Furthermore, in most cases decalcification procedures are necessary to investigate the samples which can potentially hamper molecular analyses. In this talk, some aspects of a pathologist’s point of view will be presented including potential clues to overcome the problems described. The application of genome wide SNP chip analyses identifying genetic signatures associated with the prognosis of patients, the role of deregulated miRNAs in osteosarcoma as well as tissue microarrays as an efficient and tissue sparing method to analyse and validate new biomarkers or specific genetic alterations using fluorescence in-situ hybridization (FISH) and immunohistochemistry will be explained and discussed. Working together and sharing resources is a key factor in osteosarcoma research and we are looking forward to this new cooperation.