

HANDBOOK FOR OSTEOSARCOMA

Updated Spring 2014

This handbook is created for surgeons who care for children with osteosarcoma, and is taken directly from COG biology and clinical protocols. The biology protocol is AOST 06B1-Collecting and Banking Osteosarcoma. There are 2 recent clinical protocols, AOST 0331-Treatment strategies for resectable osteosarcoma (closed Oct 2013), and AOST06P1-Feasibility in treatment of newly diagnosed metastatic osteosarcoma (closed Apr 2012). This handbook also draws references from study AOST0221 (closed Dec 2013) for first pulmonary recurrence of osteosarcoma.

The handbook extracts and arranges relevant information for surgeons into a single document, designed to streamline the delivery of pertinent information on issues that you will encounter when treating your patient.

The handbook begins with a One Minute Review, which outlines bare minimum facts necessary before going to the operating room, including staging, biopsy, and resection. There follow background and guidelines from the biology protocol, common surgical principles for all clinical protocols (biopsy, resection, and metastatic disease) and then other materials from the clinical protocols. Surgically relevant information is delivered verbatim with citation. The table of contents at the left margin indicates bookmarks for a given section of this document, so you can click on that topic for immediate review. Questions are encouraged, and directed to the Surgery Study members listed below. The Chair of the Bone Tumor Surgery Steering Committee is Lor Randall

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This summary seeks to make life easier for the surgeon and facilitate compliance with protocol guidelines. This Web site will be updated when protocols are amended. Any and all suggestions for improvement are welcome.

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ONE MINUTE REVIEW

STAGING: Enneking' Classification, based on grade, site, and metastases

Grade	G1-benign	G2- low grade	G3-high grade
Site	T0-benign, within capsule		
	T1- malignant tumor within compartment		
	T2- lesion spread beyond anatomic compartment		
Metastasis	M0- no metastases	M1- metastases	

Stage	Grade	Site	Metastasis
IA	G1	T1	M0
IB	G1	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
III	G1 or G2	T1 or T2	M1

OPERATIVE STAGING BASED ON AJCC Criteria on basis of surgical resection

R0- Complete resection, microscopic clear margin

R1- Macroscopic complete resection, microscopic margin positive

R2- Intralesion resection, gross residual disease

Biopsy:

Obtain maximum, prudent, amount of viable tumor. (≥ 1 gm)

Open Biopsy strongly recommended. Core biopsy must procure sufficient tumor, and not contaminate completeness of definitive surgery

Enrollment on Biology protocol AOST06B1 suggested, not required.

Placement of a double lumen central venous access device

Definitive Surgery:

Timing from start of Chemo: Week 11 (AOST0331) or Week 12 (AOST06P1)

Local control:

Macroscopically complete surgical resection, prefer wide or radical margins.

No role for marginal or intralesional surgery

Limb sparing surgery if possible, mutilating if necessary; if tumor poor histologic responder, then caution with limb sparing resection.

If unable to obtain surgical local control, XRT with guidelines provided;

Patient off protocol, but followed. Consult Bone Tumor Study member.

Limb Sparing Reconstruction

Endoprosthesis (distal femur, proximal tibia) or modular prosthesis (proximal femur), based on clinical experience/opinion of ortho oncologist.

Proximal humerus-prosthesis, vascularized graft, turn down of clavicle.

Diaphyseal tumor-biologic reconstruction preferred. Pelvis-high risk.

Metastatic Disease:

Pulmonary Metastatic Disease: Complete resection of all primary metastases

Timing: Between Week 12 and Week 26.

Classification: 3 or more lesions >0.5cm, or 1 lesion >1cm

Recommended- Thoracotomy with manual palpation of both lungs, even if imaging suggests unilateral disease. Avoid thoracoscopy.

AOST06B1: CHILDREN'S ONCOLOGY GROUP PROTOCOL FOR COLLECTING AND BANKING OSTEOSARCOMA SPECIMENS

Background and Rationale

2.0 BACKGROUND AND RATIONALE

Since the introduction of adjuvant chemotherapy two decades ago, the survival of patients with osteosarcoma has not improved significantly, with several studies reporting EFS in the 70% range. Further alterations in chemotherapy are likely to involve escalation in dose-intensity and additional new agents. As these result in heightened therapeutic risk, it will become increasingly important to be able to predict, at the time of diagnosis, which patients are at increased risk of treatment failure with the current standard therapy. There has been no satisfactory method of predicting, at the time of diagnosis, which patients are likely to do poorly and which are likely to do well. The hypothesis underlying this study is that outcome in these diseases may be related to levels of expression of various genes which influence tumor properties such as growth rate, invasiveness, metastasis and, most importantly, response to chemotherapy. The patterns of tumor gene expression can be measured at the time of initial diagnosis. In addition, the survival for patients who present with metastatic disease remains very discouraging, generally less than 25%. The survival is also poor for those patients who relapse after completion of therapy. For these patients, new therapeutic approaches are desperately needed. Several of the determinants that will be explored are discussed in the following paragraphs:

2.1 Drug Resistance Related Genes

2.1.1 MDR/MRP Expression

The potential role of these drug efflux systems as a determinant of drug responsiveness is known and their influence as a prognostic indicator in osteosarcoma has been suggested by recent studies. P-glycoprotein is a transmembrane ATP-dependent protein encoded by the MDR1 gene, which is responsible for the efflux of numerous chemotherapeutic agents including doxorubicin. In a study of 92 OS tumor samples 30 percent were found to have expression of p-glycoprotein by immunohistochemistry. Elevated p glycoprotein was associated with a decreased probability of event free survival ($p=0.002$). This study failed to show a correlation between p-glycoprotein expression and histologic response to preoperative chemotherapy or histologic response and outcome. The correlation of histologic response to preoperative chemotherapy has been demonstrated in many previous large studies. The utility of p-glycoprotein expression as a prognostic indicator needs to be verified. Further elucidation of the incidence of p glycoprotein overexpression may also allow prioritization of therapeutic trials of MDR reversal agents. Numerous compounds capable of reversing the MDR phenotype have been identified (verapamil, cyclosporine) and less toxic analogues of these drugs are currently in phase testing (SDZ PSC 833). P glycoprotein is a member of the ATP-binding cassette superfamily of membrane transport proteins. A more recently identified member of the same family, multidrug resistance-associated protein (MRP) is also capable of effluxing natural compounds such as doxorubicin and etoposide. Transfection of MRP into cell lines results in the development of resistance to these agents in a similar fashion as p glycoprotein. MRP has been implicated in drug resistance and outcome in neuroblastoma, lung cancer and some types of leukemia. MRP has not been studied as a prognostic factor in OS. Since any prognostic indicator is only valid within a particular therapeutic context and other studies have failed to demonstrate the relationship

between p-glycoprotein expression and outcome, this measurement will be made and correlated with results of our current therapeutic trials. P-glycoprotein expression will be measured using multiple modalities to clarify prior discrepant results.

2.1.2 Methotrexate Transport and Metabolism

Methotrexate is an important component of therapy in the current protocols for osteosarcoma supported by significant in vitro evidence that methotrexate is an active agent in the treatment of this disease. Resistance to methotrexate can occur through a variety of mechanisms including impaired transport of the drug into the cell via the reduced folate carrier, dihydrofolate reductase enzyme amplification, and diminished intracellular accumulation secondary to decreased polyglutamylation. Osteosarcoma may have an intrinsic methotrexate transport defect or dihydrofolate reductase enzyme amplification which can be overcome by achieving a high extracellular drug concentration. Identifying relevant mechanisms of resistance may suggest therapeutic trials of newer antifolates which can overcome these resistance mechanisms. Preliminary data has shown that decreased expression of the reduced folate carrier is a major mechanism of methotrexate resistance in osteosarcoma. Reduced folate carrier expression in that study correlates with histologic response to preoperative chemotherapy. Based on this observation trimetrexate and leucovorin are being tested in Phase II clinical trials for osteosarcoma. Further information regarding mechanisms of MTX resistance in osteosarcoma is required.

2.1.3 Topoisomerase II levels

Among the agents utilized currently in various protocols for pediatric bone tumors are doxorubicin and etoposide. Both of these agents appear to function by stabilizing the intermediate complex between DNA and topoisomerase II (Topo II), blocking Topo II function and also leading to DNA damage proportional to the level of Topo II present. Topo II levels are thus a determinant of response to these and other agents which utilize this mechanism.

2.1.4 Bcl Family Members (BCL-2, Bcl-XL, Bax, ML-1)

These two proteins are important control elements of the apoptosis pathway which may function together or in opposition to each other. Their balance may determine how readily a tumor cell responds to chemotherapy-induced DNA damage by initiating the programmed cell death pathway.

2.2 Tumor Suppressor Genes and Oncogenes

2.2.1 Rb/p53

The tumor suppressor genes p53 and retinoblastoma (Rb) are altered in a significant proportion of osteosarcoma tumor samples. The alterations in p53 observed in osteosarcoma consist of point mutations (occurs in 25-30%), gross gene rearrangements (occurs in 10-20%), and loss of one 17q allele (occurs in 75-80%). The p53 protein has an important regulatory role in the control of cell cycle progression and the activation of apoptosis, which influences the rate of cell growth as well as response to chemotherapy. Downstream components of this pathway p16 and p21 will

also be studied. The presence of p53 mutations has been associated with a poor prognosis in a variety of malignancies such as colorectal adenocarcinoma and soft tissue sarcoma. Further studies of the incidence of p53 derangements in osteosarcoma may also allow prioritization of therapeutic strategies designed to introduce wild type p53 into tumor cells. Approximately 60 percent of osteosarcoma tumors will have loss of heterozygosity at 13q the site of Rb. Gross structural rearrangements of the Rb gene are present in approximately 30 percent of osteosarcoma tumors, but mutations are rare, occurring in less than 10 percent. Patients with the hereditary form of retinoblastoma have an unusually high frequency of osteosarcoma secondary to alterations in the Rb tumor suppressor gene, thus implicating Rb in the tumorigenesis of osteosarcoma. Rb, like p53 has an important role in controlling the progression of a cell through the cell cycle. A retrospective study of 47 patients with osteosarcoma identified loss of heterozygosity of the Rb gene as a poor prognostic factor.

2.2.2 ErbB-2

The c-erbB-2 proto-oncogene (also called Her2/neu) encodes a protein structurally homologous to the epidermal growth factor receptor although its actual ligand has not yet been identified. Overexpression of human c-erb-2 induces malignant transformation of rodent fibroblasts. In a European study of 26 osteosarcoma tumor samples 42 percent expressed c-erbB-2. No amplification of the c-erbB-2 gene was detected. Our preliminary results have confirmed that the frequency of ErbB-2 expression is approximately 45%. Protein expression was associated with a poor prognosis. Patients whose tumors expressed c-erbB-2 had a higher risk of developing pulmonary metastasis within 6 months after initial diagnosis and poor response to chemotherapy. These results require confirmation in the context of larger therapeutic trials. In addition, use of the clinically available anti-Her2/neu antibody together with standard chemotherapy dramatically improves the response rate in breast cancer. A similar approach might be effective in osteosarcoma.

2.2.3 MDM2

The MDM2 protein is a regulator of p53 function and high levels of expression may result in functional inactivation of the p53 protein. MDM2 amplification can therefore result in functional p53 inactivation in the absence of p53 genomic alterations. In a retrospective study of 28 high grade osteosarcoma samples amplification of MDM2 was present in 14 percent. Amplification of MDM2 was observed more frequently in metastatic or recurrent osteosarcoma as compared to primary osteosarcoma ($p=0.02$). In a recently published larger study ($n=83$) performed by the same group, the frequency of MDM2 amplification was lower (6.6%) but the association with recurrent and metastatic disease persisted ($p<0.02$).

2.2.4 p16 and p21

These are critical components of the cell cycle regulatory system which also includes p53 and Rb. The p21 protein is a downstream mediator of p53 function. These proteins inhibit the activity of the cyclin DCDK4 complex which is necessary for cell cycle progression through the G1/S transition. This G1/S transition is an important regulatory checkpoint prior to the start of DNA replication. Tumor cells, in order to continue proliferating, require a mechanism to pass through this checkpoint. Numerous tumors have been identified which have alterations in the p16 or p21 genes including but not limited to melanoma, leukemia, lymphoma, ovarian, renal and lung carcinomas. In a retrospective study of 29 osteosarcoma samples large p16 gene deletions were

detected in two samples. In contrast, no p16 point mutations were identified in the 41 OS tumor samples tested. No study of p21 alterations in OS has been reported to date. Studies of p16 and p21 in addition to potentially identifying a prognostic indicator, may allow prioritization of future clinical trials. Drugs have been developed, such as flavopiridol, which bind to CDK2 and CDK4 resulting in their inactivation replacing the function of a mutant or deleted p16 or p21 gene. Demonstration of frequent p16 or p21 alterations in OS would suggest a clinical trial of one of these compounds may be warranted. These pathways are clearly of great importance as prognostic indicators and/or therapeutic targets.

2.2.5 LOH at 3q and 18q

Other sites of frequently observed loss of heterozygosity in OS such as 3q and 18q may contain other tumor suppressor genes which have not yet been identified and may also be tested as potential prognostic indicators. Loss of heterozygosity of 3q is observed in over 70 percent of OS tumor samples and the location of the potential tumor suppressor gene has been localized by chromosomal mapping to be between 3q26.2-3q26.3. Additional evidence that this region may be involved in OS is the mapping of a bone dysmorphism syndrome Brachmann-Delange to the same region. Preliminary data in a limited number of samples suggests there may be a correlation between loss of heterozygosity at 3q and the development of pulmonary metastases in patients who present with localized disease ($p=0.07$, unpublished observations, Marc Hansen). No study correlating loss of heterozygosity at either the 3q or 18q locus with outcome has been published to date.

2.2.6 C-sis, Gli, and C-fos Amplification or Overexpression

C-sis encodes a chain of the platelet-derived growth factor, PDGF. C-sis transcripts are detected in human osteosarcoma cells. In spontaneously arising canine osteosarcoma, an excellent model for the human disease, the c-sis gene is amplified, although at modest levels of 2-3 fold. The potential for c-sis amplification or overexpression to serve as a prognostic indicator in osteosarcoma has not been explored. The gli gene, so named because of its discovery in glioblastoma, is related to a known regulatory gene for development in *Drosophila*, but is unrelated to other known oncogenes in mammalian cells. A survey of pediatric sarcomas revealed amplification of gli in rhabdomyosarcoma and in an osteosarcoma with unusual very primitive histologic features. Although the number of samples investigated in this study was relatively small, it appeared that gli amplification was an infrequent event in pediatric mesenchymal tumors. In considering whether gli should be included in the list of studies to be done here, we took into account the fact that an infrequently occurring but powerful prognostic indicator may yet be extremely valuable in overall management. A relevant example is the rare finding of t(9,22) translocations in pediatric ALL. The c-fos proto-oncogene encodes a protein which forms heterodimers with certain other proteins (jun proteins). These heterodimers are transcriptional regulators of specific target genes which are involved in cell growth, differentiation and transformation. There are several important links to bone tumors, particularly osteosarcoma. Fos/jun heterodimers play a physiologic role in regulating normal bone metabolism. Osteosarcoma can be induced in rodents by injection of a viral homologue of c-fos. Transgenic mice which overexpress c-fos develop osteosarcoma. A study of 30 osteosarcoma patient samples revealed that 61% overexpressed c-fos; however, there has yet been no study of whether c-fos overexpression correlates with prognosis.

2.2.7 SV-40 T-antigen Sequence

Recently, sequences corresponding to the T-antigen of SV-40 virus were detected in human osteosarcomas. The origin and role of these in osteosarcoma is unknown but their frequency and predictive potential should be investigated.

2.2.8 myc/Ras

The myc gene product is involved in the regulation of cell proliferation, DNA replication and in the regulation of transcription of some specific genes. myc overexpression can inhibit differentiation of some tumor types. In a retrospective study of 27 OS tumor samples 7 percent were identified as having myc amplification. No cases of myc gene rearrangement were observed. The Ras protein is involved in signal transduction pathways. When mutated the Ras protein loses the ability to become inactivated and it therefore stimulates growth and inhibits differentiation autonomously. Activating Ras mutations can be found in as many as 15-20% of human tumors including pancreas, colon, lung, thyroid tumors and in myeloid leukemias. An osteosarcoma cell line with a mutated Ras has been identified and reported. Limited studies of OS tumor samples looking for specific Ras mutations have been performed and have failed to identify any Ras mutations. A further attempt to determine if Ras mutations occur in OS is warranted as it may identify a potentially useful therapy for a subset of OS patients with Ras mutations. New drugs which inhibit farnesyl-protein transferase which is necessary for Ras processing have been developed. These drugs which are currently entering clinical trials may be of benefit to patients whose tumors possess Ras mutations.

2.3 Genes Related to Environmental Interactions

2.3.1 Metalloproteinase Expression

The metalloproteinases include a number of activities responsible for lysing extracellular matrix proteins either normally as in tissue growth and remodeling or malignantly as part of invasion and metastasis. Metalloproteinase activity is thus likely to be an important component of the invasive and/or metastatic phenotype. Metalloproteinase inhibitors have been developed and are entering early phase clinical trials. As these might well be effective agents in pediatric bone tumors, we plan to explore the expression of their putative targets in these tumors. Specifically we will examine the expression of matrix metalloproteinase 1, 2 and 9 as well as tissue inhibitors of metalloproteinases 1 and 2. It is these proteins and the ratios of the proteins which have been implicated as prognostic factors in a variety of other malignancies. We will attempt to identify investigators to study the relationship of metalloproteinase expression with the plasminogen-plasmin activator system. These studies will be of particularly high priority in the study of metastatic samples.

2.3.2 The MET Pathway

The c-met proto-oncogene codes for a cell surface glycoprotein which is the receptor for a stimulatory factor known either as hepatocyte growth factor or scatter factor. Stimulation of the c-met gene product by its ligand induces a multiplicity of cellular responses, including cell division (mitogenic response), upregulation of the microtubular cell motility system (motogenic response) and synthesis of surface binding receptors for peptide hydrolases, key elements of the matrix lytic system (matrilytic response). Together these responses include all of the features which, in the uncontrolled state, are associated with aggressive, highly metastatic tumors,

growth, motility, and ability to escape from (and gain entrance to) extracellular matrices. These properties are characteristics of osteosarcoma, which are aggressive, invasive, highly metastatic tumors. c-met overexpression has been correlated with poor outcome in breast cancer and several other adult tumors. c-met is highly expressed in 60% of human osteosarcomas, but has not been studied as a prognostic indicator. GNT-V is an upstream regulator of the MET pathway. It is a Golgi-associated aminoglycosyl transferase. Among the multiplicity of its effects is the stabilization of Matriptase, the activator of HGF (Scatter Factor). Transfection of GNT-V into the non-metastasizing human tumor cell line MKN45 induces the metastatic phenotype (Ihara et al (2002) J. Biol. Chem. 277 (19:16960-67)

2.3.3 IGF-I

Based on the observation that the peak age incidence of OS coincides with a period of rapid bone growth, it has long been believed that external influences such as the levels of circulating growth hormone play a role in the etiology of OS. Insulin like growth factor I (IGF-I) is a polypeptide synthesized predominantly in the liver where its production is regulated by the levels of growth hormone. It is also synthesized in a number of extrahepatic sites where its regulation is unclear. IGF-I has been demonstrated to have an important role in normal bone growth, turnover and metabolism. OS cell lines have been demonstrated to express IGF-I receptor and are dependent on IGF-I for growth in tissue culture. Human OS tumors growing as xenografts in athymic mice are inhibited by antagonists of growth hormone releasing hormone. The serum and receptor levels of IGF-I will be investigated as potential prognostic indicators. These studies may also allow a prioritization of clinical trials of inhibitors of growth hormone in the treatment of OS. A number of drugs including somatostatin and its longer acting analogues (sandostatin) which inhibit growth hormone are being investigated in the treatment of a variety of malignancies.

2.3.4 Ezrin

Ezrin is an actin-cytoskeleton linker, which is believed to be necessary for osteosarcoma metastasis. Once established, metastatic cancers are generally refractory to treatment and are the primary cause of morbidity and mortality associated with cancer progression. Khanna C, et al, used a genome wide approach to identify metastasis-associated genes in osteosarcoma. From this genomic data, ezrin was selected for further study based on its role in physically and functionally connecting the actin cytoskeleton to the cell membrane. By imaging metastatic cells in the lungs of mice it was demonstrated that ezrin expression provided an early survival advantage for cancer cells that reach the lung. Potentially explaining this early survival advantage, reduction in both AKT and MAPK phosphorylation and activity was found when ezrin protein was suppressed in osteosarcoma cells. High ezrin expression in canine tumors was associated with the development of metastases. Consistent with this data a significant association between ezrin expression and favorable outcome in pediatric osteosarcoma patients has been identified in a limited sample set. Verification of this result in the context of a larger clinical trial is warranted.

2.4 Basic Tumor Biology

2.4.1 Telomerase

The recently described DNA polymerase system is responsible for maintaining the length of the telomeric portion of each chromosome in mammalian cells. In the absence of telomerase expression, chromosomes shorten with each replication cycle until a critical point is reached

when replication is no longer possible. Telomerase expression is thus a critical regulator of the number of replications a cell may undergo. Its expression has been negatively correlated with prognosis in several adult tumors. It has not as yet been studied in pediatric bone tumors.

2.4.2 Ploidy

Many random cytogenetic abnormalities are present in osteosarcoma tumor cells. Ploidy has been investigated in numerous prior studies of osteosarcoma as a prognostic factor. Since any prognostic indicator is only valid within a particular therapeutic context, this measurement will be made and correlated with results of our current therapeutic trials.

PATIENT ELIGIBILITY (AOST06B1 4.2.1)

All osteosarcoma patients seen at COG institutions are eligible. This includes:

- a. newly diagnosed patients
- b. patients with recurrent disease who were not enrolled at the time of diagnosis

Patients are **not** required to enter a therapeutic study to enroll on AOST06B1.

There are no age limitations.

GUIDELINES FOR PROCURING SAMPLES (AOST06B1 5.0)

Since institutional surgeons and pathologists must be active participants in this protocol, investigators should circulate and discuss this protocol with their pathology and surgical colleagues. Referring physicians should be encouraged to send the patient unbiopsied to the participating institution. Surgeons should obtain the maximum amount of tumor that is prudent at the time of biopsy or resection. The resected specimen should be placed in a sterile container, covered with saline-soaked gauze, and sent to the pathologist's attention immediately. Pathologists must maintain the sterility of tumor specimens, and allocate as generous an amount as possible for the biological studies and tumor bank, while retaining sufficient tissue for clinical management.

Specimen Procurement Kits: The Specimen Procurement Kits (provided by the BPC upon request) are constructed to allow shipment of frozen (on dry ice) and ambient (room temperature) specimens in the same container. To order kits for this study please call the BPC at (800) 347-2486. The kits include formalin-filled containers for fixed tissue, vials for serum and plasma, truncated embedded molds for tumor frozen in OCT, and (upon request only) a tube of media for fresh tissue that is to be collected for specimens for Dr. Gorlick. Also included in each kit are instructions, mailing labels, secondary diagnostic shipping envelopes with absorbent material and a Federal Express air bill (pre-billed to the BPC). Please use these kits only for sending specimens to the BPC. In addition, a Diagnostic Specimen Bag and a blank Federal Express air bill will be provided for sending the fresh specimens to Dr. Gorlick. Label specimens with the patient's BPC Number, specimen type and collection date. Include a specimen transmittal form with each shipment.

5.2 Requested Specimens

5.2.1 At Enrollment

As only a portion of the planned studies can be performed on paraffin embedded tissue, a good faith attempt to obtain the following tissues should also be made. It is recommended that whenever consistent with good patient care, an open biopsy be performed:

- Viable tumor tissue (> 1 gram) from the biopsy, definitive surgery, and, if applicable, recurrence:
 - a) Half the tissue should be snap frozen and sent on dry ice to the Biopathology Center (BPC).
 - b) Half should be placed in sterile media and sent to Dr. Richard Gorlick.

5.2.2 At Definitive Surgery, Recurrence

For patients who are enrolled at the time of initial diagnosis but then have a definitive surgery or develop recurrent disease, submission of additional samples is strongly encouraged. Re-enrollment is not required. The samples should be clearly marked as “definitive surgery” or “recurrence” samples, and the unique BPC number used.

- Paraffin embedded block is preferred, and every effort should be made to submit specimens in this form. The block will be retained at the BPC unless return is requested by the submitting institution. Only if a block is not available should institutions submit 30 unstained slides.
- Pretreatment blood consisting of:
 - 5 mL serum **and**
 - 10 mL plasma **and**
 - 10 mL heparinized whole blood
- Viable tumor tissue (> 1 gram) from the biopsy, definitive surgery, and, if applicable, recurrence:
 - c) Half the tissue should be snap frozen and sent on dry ice to the Biopathology Center (BPC).
 - d) Half should be placed in sterile media and sent to Dr. Richard Gorlick.

5.2.3 At Autopsy

Submission of tumor samples from autopsy is strongly encouraged. Re-enrollment is not required. The samples should be clearly marked as “Autopsy” samples, and the unique BPC number used.

- Paraffin embedded block is preferred, and every effort should be made to submit specimens in this form. The block will be retained at the BPC unless return is requested by the submitting institution. Only if a block is not available should institutions submit 30 unstained slides.
- Viable tumor tissue (> 1 gram).

SURGICAL GUIDELINES- AOST0331 Section 14.0, AOST06P1 Section 15.0

Venous Access

8.0 Supportive Guideline

The presence of a double lumen central venous access device (VAD) is recommended but not required.

BIOPSY

14.1 Biopsy

The diagnosis of high-grade osteosarcoma must be verified histologically within 14 days of study enrollment. In order to ensure appropriate biopsy techniques and an appropriate evaluation of the obtained material, it is strongly recommended that biopsies should only be performed in specialized centers. Open biopsy may be performed in order to obtain sufficient material for rapid central review and ancillary studies. The biopsy specimen should be forwarded to the institutional pathologist without prior fixation. Enrollment on a COG osteosarcoma specimen collection study is strongly encouraged.

14.2 DEFINITIVE SURGERY

For osteosarcoma, surgery is the local treatment of choice. Complete surgical removal of all affected sites is mandatory whenever feasible. Rapid central review will be done on the surgical specimen.

14.2.1 Definitive Surgery of the Primary Tumor

Surgery of the primary tumor is scheduled for 11 weeks (12 weeks for AOST06P1) after the commencement of chemotherapy. Surgery should be performed in a manner which guarantees wide or radical margins according to Enneking's classification. While it is most often possible to reach such margins without sacrificing the affected limb, mutilating surgery may become necessary if this is not the case. The indication for limb salvage must be made with particular caution if a poor tumor response to preoperative chemotherapy is anticipated by clinical investigations or appropriate imaging studies. Marginal or intralesional surgery should be avoided whenever possible and must be restricted to situations where wide or radical margins are not achievable by any means. As inappropriate surgery may easily lead to local recurrence and death in otherwise curable patients, it is strongly recommended that osteosarcoma surgery should only be performed in specialized centers.

14.2.2 Definitive Surgery Guidelines

14.2.2.1. Prior to definitive surgery the following parameters are recommended:

Neutrophils $>1.0 \times 10^9/L$

Platelets $> 80 \times 10^9/L$

14.2.2.2 Indications for limb salvage surgery:

- Tumor resectable with wide margins
- Reconstruction possible and likely to be successful
- Patient aware of risks/benefits of limb salvage

14.2.2.3 Indications for amputation:

- Inability to completely resect the tumor without leaving residual disease
- Extensive involvement of neurovascular bundle
- Patient preference

There will be many situations where the decision is not easy, in particular when there has been a poor response to chemotherapy, there is extensive soft tissue involvement and the tumor is adjacent to the main neurovascular bundle. In these situations seek a second opinion from one of the main surgical centers.

14.2.3 Reconstruction after limb salvage surgery

There are many types of limb salvage reconstruction available. Remember that the principle aim of the surgeon is to completely resect the tumor with wide margins. This principle should never be sacrificed in order to make limb salvage reconstruction easier. The patient will want a reconstruction that will function well and have few complications. In some situations an amputation may give a better and more predictable result than attempts at reconstruction (e.g. distal tibia). The following reconstruction options represent standard treatment but are NOT meant to exclude other options:

14.2.3.1 Distal Femur – in most cases use of an endoprosthesis will give a good result. If the tumor involves the knee joint an extra-articular resection should be carried out.

14.2.3.2 Proximal Tibia - use of an endoprosthesis will work well if the extensor mechanism is reconstructed. A gastrocnemius muscle flap should be part of the soft tissue reconstruction.

14.2.3.3 Proximal Femur – modular endoprostheses work well. Because of the significant risk of dislocation a large unipolar or bipolar head is recommended.

14.2.3.4 Proximal Humerus – reconstructive options include the use of a prosthesis, a fibula graft (vascularized) or a turn down of the clavicle (claviculo pro humero).

14.2.3.5 Pelvis – all surgical reconstructions are high risk and should be carried out at a center with appropriate expertise.

14.2.3.6 Diaphyseal tumor – When the joints can be spared above and below a tumor in a long bone then a biological reconstruction is preferred – either using an allograft or an autograft (or a combination)

14.2.3.7 Young children with long bone tumors – extendable endoprostheses have proved useful but have a significant risk of complications. Families must be fully informed about risks/benefits and the inevitability of the need for further surgery. Rotation plasty should be considered in these cases.

IF THERE IS INSUFFICIENT LOCAL EXPERTISE, REFER TO A SURGICAL REPRESENTATIVE ON THE COG COMMITTEE

14.2.4 Surgery of pelvic and other axial tumors

Osteosarcomas arising in the axial skeleton (excluding craniofacial bones) which are deemed resectable with curative intent are eligible for inclusion in this protocol. Subsequent surgical management of such tumors may include amputation (fore or hind quarter for shoulder girdle and pelvic tumors) or complex reconstruction. The chosen approach should be anticipated to achieve the safest oncological margin and at least macroscopic resection.

14.2.5 SURGERY OF PRIMARY METASTASES

If primary metastases are present, all of these must also be resected completely, regardless of their number and site, if the affected patient is treated with curative intent. Resection is strongly recommended for patients felt to have definite or possible pulmonary metastases at initial diagnosis. The preferred timepoint for surgery of primary metastases may be between protocol weeks 11 and 20, but other dates may be chosen at the discretion of the treating physicians. For pulmonary metastases, thoracotomy with manual exploration of both lungs is strongly recommended, even when imaging studies suggest unilateral disease. The use of thoracoscopic techniques is strongly discouraged, as they lack sensitivity and may be associated with an increased risk of intraoperative tumor dissemination. In order to avoid complications associated with delayed methotrexate excretion due to third-spacing into pleural effusions, thoracotomy should not be followed by high-dose methotrexate, but rather by other chemotherapeutic agents.

THORACIC SURGERY GUIDELINES AOST0221 (CLOSED) SECTION 4.3

The overall objective of pulmonary metastasectomy is to completely resect all pulmonary metastatic disease. This includes nodules that are detected by CT imaging as well as occult lesions found only at surgical exploration. There is evidence that a significant proportion of patients with apparent unilateral lung metastases may, in fact, have occult contralateral metastases.

AOST0221 4.3.1 Surgical Recommendations

4.3.1.1 Unilateral Metastases.

For patients with presumed unilateral pulmonary metastases by CT imaging, a thoracotomy should be performed and all visible and palpable disease resected. One-lung ventilation anesthetic techniques should be used to allow sequential inflation and deflation of the affected lung to allow careful identification of all disease. For most lung nodules, an automated surgical stapling device (TA or GIA) is recommended to provide a margin of normal lung tissue around the nodule. When this is not feasible, due to location or other reasons, cautery excision of the lesion is acceptable. Thoracoscopy, or VATS (video-assisted thoracic surgery), is not allowed. The majority of evidence shows that complete resection of osteosarcoma pulmonary metastases requires palpation of the lung, which is not possible thoracoscopically. In patients that have unilateral pulmonary metastases confirmed histologically after thoracotomy, consideration should be given to contralateral thoracotomy and resection of occult disease if found. Whether a contralateral thoracotomy is performed or not, the incidence of occult contralateral disease and the effect on disease free survival (DFS) will be recorded. Contralateral thoracotomy is not mandatory, however, in this situation.

4.3.1.2 Bilateral Metastases.

For patients with imaging evidence of bilateral lung metastases, complete resection of all known and occult lung lesions is again the goal. In general, acceptable surgical alternatives include bilateral thoracotomy, either performed during a single anesthetic or done in a staged fashion, or median sternotomy. For this specific protocol, bilateral staged thoracotomies are preferred to allow biologic assessment of inhaled GM-CSF. Median sternotomy is most suitable for patients with small, peripheral nodules and in patients with limited posterior pulmonary metastatic disease. Thoracoscopic resection, or VATS, is not allowed. One-lung ventilation techniques are critical to complete resection of bilateral metastatic disease and should be planned in collaboration with the anesthesiologist preoperatively.

AOST0331: RANDOMIZED TRIAL TO OPTIMIZE TREATMENT STRATEGIES FOR RESECTABLE OSTEOSARCOMA BASED ON HISTOLOGIC RESPONSE TO PREOPERATIVE CHEMOTHERAPY

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

Primary Aims:

1.1 In a randomized setting, to examine whether the addition of ifosfamide and etoposide (IE) to postoperative chemotherapy with cisplatin, doxorubicin and methotrexate improves the event-free survival for patients with resectable osteosarcoma and a poor histological response to 10 weeks of pre-operative chemotherapy.

1.2 In a randomized setting, to examine whether the addition of pegylated interferon alfa-2b as maintenance therapy after post-operative chemotherapy with cisplatin, doxorubicin and methotrexate improves the event-free survival for patients with resectable osteosarcoma and a good histological response to 10 weeks of pre-operative chemotherapy.

Secondary Aims:

1.3 To investigate whether the addition of IE to post-operative therapy for poor responders, and the addition of Peg-Intron as maintenance therapy for good responders, leads to an improvement in the following outcomes:

- a. Overall survival
- b. Short-term toxicity
- c. Long-term toxicity
- d. Quality of life

1.4 To investigate whether the addition of IE to post-operative therapy for poor responders, and the addition of Peg-Intron as maintenance therapy for good responders, leads to an improvement in event-free and overall survival in patients with localized osteosarcoma at entry.

1.5 To investigate whether biological or clinical correlates to histological response and outcome can be identified by encouraging enrollment on a COG osteosarcoma specimen collection study.

1.6 To examine the outcome of the entire cohort of patients.

ABSTRACT

EURAMOS 1 is a joint protocol of four of the world's leading multi-institutional osteosarcoma groups (COG, COSS, EORTC/MRC, SSG). The collaboration's main aim is to optimize the treatment of patients suffering from osteosarcoma. The EURAMOS 1 trial is open for all patients with resectable high-grade osteosarcoma of the limbs or axial skeleton, whether the tumor is localized or primarily metastatic, who are considered suitable for neo-adjuvant chemotherapy. The trial takes into account the strong prognostic value of tumor response to preoperative chemotherapy and divides patients accordingly. All patients registered will receive a standard three-drug induction regimen consisting of 2 cycles of cisplatin and doxorubicin along with four cycles of methotrexate (**MAP**). After recovery from chemotherapy, patients then proceed to surgical resection. Post-operative therapy is determined by the histological response of the tumor. Good responders (< 10% viable tumor) will be randomized to continue with **MAP**, or receive pegylated interferon alfa-2b as maintenance therapy after MAP (**MAPifn**). Poor responders ($\geq$ 10% viable tumor) will be randomized to continue with **MAP** or to receive the same regimen with the addition of ifosfamide and etoposide (**MAPIE**). Event-free survival is the primary endpoint.

Patient Eligibility Section 3.2.1 AGE

Patients must be $\geq$ 5 years and $\leq$ 40 years on date of diagnostic biopsy.

17.0 Imaging Studies required and Guidelines for obtaining.

17.1.1 Imaging at Presentation and immediately prior to surgery

Site	Anatomic Imaging	Functional Imaging
Primary, bone metastases	AP/lateral radiographs	
Primary, bone metastases	MRI with gadolinium	
Whole Body		MDP bone scintig, +SPECT of lung if pul mets suspected
Whole Body		Thallium Scintigraphy
Whole Body		FDG-PET
Chest	CT scan	
Chest	AP/lateral radiographs	

Definition of lung metastases: minimum criteria determined by spiral CT scanning are 3 or more lesions which are $\geq$ 5mm in maximum diameter or a single lesions $\geq$ 1 cm. These patients will be classified as having "certain" pulmonary metastases. Scans of patients registered as having metastatic disease with fewer or smaller lesions will be classified as "possible" metastatic disease. Images may be requested for central review by the imaging committee. Additionally, institutions may request central review.

Definition of bone metastases: must include confirmation of bone scintigraphy or plain radiograph abnormalities either by MRI or biopsy or both.

17.1.2 Baseline Imaging after surgery:

Site	Anatomic Imaging	Functional	Timing
Primary/bone metastases	AP/lateral radiographs		2wks from surgery
Primary/bone metastases	MRI with gadolinium		

17.1.3 Surveillance Imaging while on Chemotherapy

Site	Anatomic Imaging	Functional	Timing
Primary/bone metastases	AP/lateral radiograph		q16wks
Primary/bone metastases	MRI with gadolinium		for symptoms
Whole Body		MDP bone scintig , +SPECT of lung if pul mets suspected	q16wks
Whole Body		Thallium scintig	if abnormal imaging
Whole Body		FDG-PET	if abnormal imaging
Chest	CT scan		q16wks if abnormal
Chest	AP/lateral radiograph		q2 months

17.1.4 Surveillance Imaging Post-Chemotherapy

Site	Anatomic Imaging	Functional	Timing
Primary/bone metastases	AP/lateral radiograph		q3months x 4 q 6 months x 4 q12 months x 2 for symptoms
Primary/bone metastases	MRI with gadolinium		
Whole Body		MDP bone scintig +SPECT of lung if pul mets suspected	q3monthsx 4 q6 months x 4 q12 months x 2
Whole Body		Thallium scintig	if abnormal imaging
Whole Body		FDG-PET	if abnormal imaging
Chest	CT scan		q3 months x4 Q6 months x 2 Then if abnmal x rays
Chest	AP/lateral radiograph		q6 months x 6

AOST06P1: ZOLEDRONIC ACID WITH CONCURRENT CHEMOTHERAPY IN THE TREATMENT OF NEWLY DIAGNOSED METASTATIC OSTEOSARCOMA

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To assess the feasibility and safety of adding zoledronic acid to the standard chemotherapy treatment of patients with newly diagnosed metastatic osteosarcoma.

1.1.2 To determine the maximum tolerated dose of zoledronic acid when used in combination with other standard chemotherapy agents to treat metastatic osteosarcoma.

1.2 Secondary Aims

1.2.1 To assess the histologic response and EFS in patients with metastatic osteosarcoma treated with standard chemotherapy and zoledronic acid compared to that of a similar cohort of patients treated on INT-0133 and CCG-7943.

1.2.2 To test whether markers of bone resorption are associated with risk for analytic event in patients with metastatic osteosarcoma.

ABSTRACT

Osteosarcoma is the most common malignant bone tumor in children and young adults. Patients with metastatic disease at diagnosis have a dismal prognosis, with a 5-year event-free survival (EFS) of less than 20% despite the use of aggressive surgical and medical therapy. Zoledronic acid, a recently FDA approved bisphosphonate, has shown promise as a treatment for osteosarcoma based on its safety profile, its enhanced potency and its potential antitumor and antiangiogenic properties. Towards the goal of improving EFS in patients with newly diagnosed metastatic osteosarcoma, this study will test the safety and feasibility of adding zoledronic acid to the standard chemotherapy backbone used in AOST0121. The AOST0121 chemotherapy regimen utilized the following agents: doxorubicin with dexrazoxane, cisplatin, methotrexate, ifosfamide, and etoposide. Zoledronic acid will be given as a 30 minute infusion once every 4-6 weeks for up to 8 doses with courses of this chemotherapy regimen. This study will determine the maximum tolerated dose (MTD) of zoledronic acid when used in combination with this standard chemotherapy regimen over a 36-week treatment period. The dose escalation plan will involve four levels of zoledronic acid and cohorts of 6 patients per level, expanding to 12 patients at the MTD to better define short- and longterm toxicities of the therapy. The initial dose of zoledronic acid will be 2.3 mg/m² (max 4 mg, dose level 2), followed by 3.5 mg/m² (max 6 mg, dose level 3) and 4.6 mg/m² (max 8 mg, dose level 4). Patients can only be enrolled in the next higher dose when the current dose has been determined to be safe. Up to 6 patients can be enrolled at 1.2 mg/m² (max 2 mg, dose level 1) while the higher dose levels are being evaluated for safety. It is estimated that this study will take 12-18 months to accrue assuming 30 patients in all (6 patients at 3 levels and 12 at the fourth, MTD level). As a secondary aim, histologic response and EFS will be measured in patients treated with zoledronic acid and compared to historical data from patients treated with essentially the same chemotherapy regimen without zoledronic acid. An additional secondary aim for this study will involve testing whether markers of bone resorption are associated with risk for analytic events.

Patient Eligibility AOST06P1 Section 3.2.1

Patients must be 40 years of age or younger.

15.0 IMAGING STUDIES AND GUIDELINES FOR OBTAINING

15.1 Osteosarcoma Imaging Recommendations

At presentation and Prior to Surgery/Local Control

Site	Anatomic Imaging	Functional Imaging
Primary, bone metastases	AP/lateral radiographs	
Primary, bone metastases	MRI with gadolinium (Pre-surgery exam within 4 wks of surgery)	
Whole Body		MDP bone scintig, +SPECT of lung if pul mets suspected
Whole Body		Thallium Scintigraphy
Whole Body		FDG-PET
Chest	CT scan	
Chest	AP/lateral radiographs (at presentation only)	

Baseline after Surgery/Local Control

Site	Anatomic Imaging	Timing
Primary/bone metastases	AP/lateral radiographs	<2wks from surgery
Primary/bone metastases	MRI with gadolinium or CT with contrast	3-4 months after local control

RADIATION GUIDELINES (AOST0331, Section 18.0)

Radiation therapy for patients on COG protocols can only be delivered at approved COG RT facilities (see Administrative Policy 3.9,)

18.1 Radiation Therapy Guidelines

As stated above, complete surgery is the local treatment of choice in osteosarcoma. Radiotherapy is reserved for situations where complete surgery cannot be achieved. Radiotherapy is, however, recommended for inoperable sites or those that could only be operated with inadequate margins. It is strongly suggested that participating institutions use the information and consulting systems set up by their respective groups before assuming inoperability, because some lesions which at first seem inoperable may turn out to be operable for specialized tumor surgeons. Further recommendations about how to proceed in specific situations may vary between groups. When radiotherapy is indicated, chemotherapy should not be interrupted for radiotherapy which is generally best deferred until the end of chemotherapy. Radiotherapy may be administered during treatment with interferon but it is not anticipated that the need will arise except in most uncommon circumstances. Chemotherapy can be continued during radiotherapy, but enhancement of radiation toxicity is likely to occur with several agents and at the radiation doses

recommended may result in severe acute and late side effects. This is of particular concern where spinal cord is in the field. High-dose methotrexate should be avoided during radiotherapy. Doxorubicin should be avoided in radiation treatment of axial tumors as intestinal toxicity will be enhanced and this agent will also increase skin toxicity. Concurrent ifosfamide should be avoided where significant volume of bladder is in the radiation field. The patients treated with *post-operative irradiation* should receive a total dose of 60 Gy in 2 Gy fractions where margins are microscopically involved and 66 Gy where macroscopic tumor tissue is left behind. For *definitive radiotherapy* of an inoperable osteosarcoma a radiation dose of 70 Gy should always be attempted. The use of intraoperative electron boost irradiation or brachytherapy by high-dose rate afterloading techniques is permitted in cases where macroscopic tumor tissues are left behind or where the surgical margins obviously are inadequate. Three-dimensional planning is required for this study. The use of IMRT is allowed. If 3D conformal planning is used, Institutions must have an approved 3D benchmark on file at QARC. If IMRT is used, the IMRT Questionnaire and Benchmark must be completed and submitted to QARC. The benchmark material is available from the QARC website (www.qarc.org).

18.1.1 Equipment

18.1.1.1 Modality

X-rays with nominal energy of 4 MV or greater. Co-60 is not allowed on this study. Proton Radiation is not allowed on this study.

18.1.1.2 Calibration

The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center (RPC).

18.1.2 Target Volume Definitions

ICRU-50 and 62 prescription methods and nomenclature shall be utilized for this study.

Gross Tumor Volume (GTV): The GTV is the gross tumor, either palpable or possible/demonstrable by imaging techniques. Its delineation should preferentially be done in collaboration with a radiologist. Clinical Target Volume (CTV): The CTV contains the demonstrable GTV and/or sub-clinical microscopic malignant disease. Original tumor extension should guide the delineation of CTV. Ideally this should be done in collaboration with the treating surgeon. In axial tumors a safety margin of 2 cm added to GTV should be attempted. For an extremity osteosarcoma a margin of 4-5 cm may be advisable. Planning Target Volume (PTV): For the purpose of this study, a margin for set up error or patient movement is to be added to the Clinical Target Volume. The PTV for this study will be 0.5 to 1.0 cm.

18.1.3 Target Dose

18.1.3.1 Prescription Point

The prescription point is at or near the isocenter. If IMRT is used, dose may be prescribed to an isodose surface that encompasses the PTV provided that the dose uniformity requirements in Section 18.1.3.5 are satisfied.

18.1.3.2 Dose Definition

Dose is specified in Gy to muscle.

18.1.3.3 Tissue Heterogeneity

Density corrections are not required, however, inhomogeneity correction for air or bone attenuation may be applied. This typically applies in the setting of CT-based treatment planning where radiation dose distributions and treatment calculations are automatically generated based upon the CT densities of the treatment-planning scan.

18.1.3.4 Prescription Dose and Fractionation

The patients treated with *post-operative irradiation* should receive a total dose of 60 Gy in 2 Gy fractions where margins are microscopically involved and 66 Gy where macroscopic tumor tissue is left behind. For *definitive radiotherapy* of an inoperable osteosarcoma a radiation dose of 70 Gy should always be attempted.

18.1.3.5 Dose Uniformity

A maximum dose variation within the PTV between 95-105% according to the dose plan should be attempted. Hot spots outside the PTV with a maximum of 110% are acceptable only if total volume is less than 10 cm³. Moreover, single *hot spots* should not exceed 5 cm³. Wedges, compensators, beam segmentation, and other methods of generating a uniform dose distribution are encouraged.

18.1.3.6 Rests/interruptions

There are no planned rests on this study. In case of holidays or machine breakdowns, the overall treatment time might be extended where the indication is adjuvant, whereas in case of macroscopic tumor tissue compensation by adding an extra fraction (separated by a minimum of 6 hours on a treatment day) should be considered. This may not be appropriate where spinal cord, brachial or lumbar plexus is in the high dose volume. Please justify in the comments any interruptions for greater than three treatment days.

18.1.4 Treatment Technique

18.1.4.1

Volume-based (CT scan) treatment planning is required in this protocol. Techniques which shield/protect normal tissue are essential providing that they do not compromise treatment of the PTV. The use of IMRT is allowed. Fields should be chosen to minimize dose to organs at risk as defined in section 18.1.5. Multiple beam techniques, both coplanar and non-coplanar may be used to achieve the objective. If the target volume extends to the surface of the patient, adequate dose coverage should be obtained using bolus material rather than a mixed beam technique. Intraoperative radiation therapy (IORT) and brachytherapy are also allowed on this study.

18.1.4.2 IORT

If IORT is delivered, the electron energy chosen must insure appropriate target dose at both the surface and at depth. The electron energy will be calculated to the 90% line. Bolus may be permitted to insure appropriate surface dose. The IORT Physics Reporting Form and RT-2 form must be filled out with IORT as a separate target if this mode of therapy is used. CT scan is required for submission with the target area and dosimetry identified on the CT study. IORT may be delivered at the time of primary surgical excision.

18.1.4.3 Brachytherapy

Both high dose rate (multiple fractions acceptable) and low dose rate techniques are permitted for this study. If multiple fractions are chosen for high dose rate, the total dose should remain as stated in Section 18.1.3.4. The dose should be calculated to a 1 cm depth or appropriate depth as defined on computer tomography. CT study with the catheters in place is strongly encouraged with dosimetry placed on the CT study for review. If CT is not available, then orthogonal images and dosimetry in at least two planes is required for submission and review.

18.1.4.2 Patient Position

Reproducible setups are critical and the use of immobilization devices is strongly encouraged.

18.1.4.3 Field Shaping

Field shaping can be done with blocks or multi-leaf collimation.

18.1.5 Organs at Risk:

All structures that may be associated with serious late toxicity should be delineated and dose-volume histograms generated. The following maximum radiation doses should be respected:

Cervical cord (more than 5 cm length): 45 Gy

Cervical cord (less 5 cm): 50 Gy

Brain tissue: 60 Gy

Optic nerve/chiasm: 50 Gy

Intestine: 50 Gy, depending on volume

Liver:

Whole liver 20Gy: If less than ¼ volume is irradiated, 50 Gy

Kidney: 20 Gy (> 1/3)

Heart: 30 Gy

Lung: 20 – 60 Gy depending on volume

Urinary bladder: 60 Gy

SURGEON RESPONSIBILITIES

The surgeon should assign an AJCC Surgical Stage at time of definitive resection.

A dictated, detailed Operative Report, including

Demographics (name, date, surgeon, pre and postop diagnosis)

Clinical Summary (age, sex, symptoms, brief outline of preop course, indications and objectives of surgery)

Narrative Survey of operation, including incision, observations, description of procedure, extent of resection, complications, specimens taken, blood loss)