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Perioperative management of patients with bone and soft tissue tumors: a narrative review

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Abstract : Perioperative management of patients with musculoskeletal tumors may be quite challenging, due to complex treatment strategies and extensive surgical excisions. We conducted a PubMed® literature search and a total of 100 articles were finally included in this non-systematic review. Preoperative assessment should focus on both patient- and tumor-related factors. General or regional anesthesia can be used in most procedures. Neuraxial and peripheral nerve blocks provide excellent analgesia, but caution is required in patients with pre-existing neurological deficits. Perioperative monitoring should be individualized. Optimal patient positioning is essential for facilitating surgery and avoiding complications, like blindness and nerve injury during prolonged prone position. Adequate, multimodal, postoperative analgesia is mandatory for efficient physiotherapy and rehabilitation. Other important perioperative considerations include thromboembolic prophylaxis, management of perioperative hemorrhage and increased vigilance during cementing for the risk of bone cement implantation syndrome. Special considerations also include free tissue transfer, tumor embolization and percutaneous techniques, such as cementoplasty and cryoablation.

Key-words : bone tumors ; soft tissue tumors ; musculoskeletal tumors ; anesthesia ; perioperative care.

Tumors of bone and soft tissue, also known as musculoskeletal tumors, comprise a group of rare disorders with different clinical presentations, treatment options and outcomes. Nowadays, five-year survival rates have significantly increased, being approximately 54% for osteosarcoma, 75% for chondrosarcoma and 50% for Ewing's sarcoma (1). Improved survival is associated with advances in diagnosis and treatment, in terms of imaging, chemotherapy and surgical modalities. Due to the complex treatment strategies and extensive surgical excisions aiming to limb preservation, the anesthetic and perioperative management of these patients has become quite challenging.

We conducted a PubMed® literature search for all types of articles published between January 1980 and March 2016 using the terms: "bone tumors", "soft tissue tumors", "musculoskeletal tumors", and "anesthesia" or "perioperative care" in all possible combinations. A total of 389 abstracts were retrieved and examined for relevance. Articles in languages other than English were used provided they had a detailed English abstract. Clinical trials were preferred, while in vitro, basic science and experimental studies were used only when clinical data were lacking. Consequently, 58 articles were found suitable. Twenty eligible articles were found by manual searching of the references in the electronically identified articles. Finally, we additionally used 22 articles with useful information on genetics, clinical features, diagnostic and therapeutic approaches. In total, 100 articles were included.

Types, diagnosis and treatment of musculoskeletal tumors

Musculoskeletal tumors are benign or malignant growths which develop within the bone or soft tissue. Although etiology is unclear, there is some evidence that genetic involvement may exist, since familial predisposition has been documented in some patients, mostly children (2). Benign tumors may be aggressive resulting in local bone destruction (bone cysts, fibrous dysplasia, osteochondromas), or recurrence after treatment (aneurysmal bone

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cysts, osteoblastoma, giant cell tumor). The term "sarcomas", coming from the greek word "σάρκα, sarka" meaning "flesh", is used for malignant tumors derived from mesenchymal cells, including bone, cartilage, fat, muscle, vessels and blood. Primary malignant bone tumors include osteosarcoma (osseous), chondrosarcoma (cartilaginous), Ewings sarcoma and myeloma (reticulo-endothelial), while metastatic tumors (usually from breast or prostate) may also develop in the bones.

Diagnosis is based on history, symptoms, physical examination and imaging studies; magnetic resonance imaging (MRI) represents the examination of choice (3). Skeletal scintigraphy and positron emission tomography (PET) are valuable in metastases identification, the latter being used additionally to evaluate treatment efficacy (4). Diagnosis is confirmed by open or closed biopsy (3). In certain types of tumors (i.e. osteosarcoma) serum biomarkers, such as C-reactive protein, are used as therapeutic indexes and in survival prediction (5).-

Treatment is chosen according to type, location, size and spread of the tumor and patient's clinical condition and may vary from palliative care to surgical excision, radiotherapy, chemotherapy and their combination. Each case requires a multidisciplinary approach (3, 6, 7). Chemotherapy may precede (neoadjuvant therapy) and/or follow (adjuvant therapy) surgery (6). Limb salvage surgery is considered whenever possible. Rotationplasty is an option associated with excellent oncologic and functional results, preferred in patients unsuitable for limb salvage surgery. Axial tumors require a more challenging surgical approach due to their anatomy and possible post-operative neurological deficits, therefore perioperative morbidity may increase (6).

Neoadjuvants have a role in osteosarcoma and Ewing sarcoma, less evidence of benefit in soft-tissue sarcoma and no benefit in chondrosarcoma. The efficacy of chemotherapy is limited in patients with soft-tissue sarcomas. Common chemotherapeutic agents currently used include methotrexate with leucovorin in combination with doxorubicin, ifosfamide and platinum. Cyclophosphamide, dactinomycin, etoposide, vincristine, anthracyclines, alkylating agents and taxanes are also used (6).

Anesthetic implications

Preoperative assessment

Apart from patient-related factors, special consideration should be given to the planned surgical procedure, tumor expansion and current treatment. Patients at high risk should be identified. Older age, type of primary tumor, higher Charlson Comorbidity Index, and blood transfusion are associated with higher morbidity in femur fractures repair due to metastatic disease (8). Chemotherapy and/or radiotherapy may have significantly affected patient's clinical condition (6). In pelvic tumors, major vessels and nerve roots may be involved; the tumor size and invasion, along with possible pelvic venous thrombosis should be assessed. Sacral tumor resection may involve laparotomy for anterior exposure followed by posterior resection and pelvic stabilization, amenable to surgical staging. According to small retrospective series, staging offers better clinical outcomes in terms of more Intensive Care Unit (ICU)-free days, ventilation-free days and less costs (9). Moreover, there is a trend towards less fluid requirements and vasopressor support (9). In single posterior approach a 40% complication rate is reported with wound complications representing the most common (10).

All possible side effects of chemotherapeutic agents should be investigated preoperatively (Table 1) (11-18). A preoperative ECG is recommended in patients who have undergone chemotherapy, even if they maintain high levels of physical activity (17). Cardiac ultrasound is more useful in cases of suspected chemotherapy-related cardiomyopathy; for example, anthracycline toxicity may initially present as diastolic dysfunction (14).

The site of radiotherapy is of particular importance. Chest wall irradiation has been associated with fibrosis, impaired capillary permeability and increased pulmonary vascular resistance, which may develop acutely or even years after exposure. Previous chest wall irradiation has been identified as a contributing factor to pulmonary edema following surgery under general anesthesia (19). Mediastinal irradiation may cause cardiotoxicity, especially when combined with cardiotoxic chemotherapeutic agents. Previous irradiation increases patient's susceptibility to anthracycline cardiomyopathy (14). Symptoms such as dry cough and dyspnea on exertion or at rest must be further investigated via pulmonary function tests. Differential diagnosis includes chemotherapy-induced lung disease, metastatic invasion, pulmonary embolism or infection.

Myelosuppression is a negative consequence of almost every chemotherapeutic agent. In regards to hemoblobin (Hb) levels, in a retrospective study of 1958 Jenovah's Witness patients undergoing

non-cardiac surgery, Hb ≤10 g/dl was associated with increased mortality, especially in patients with cardiovascular disease (20). The Network for Advancement of Transfusion Alternatives (NATA) recommends that elective orthopedic patients should have an Hb level determination as close to 28 days before surgery as possible (Grade 1C) (21). Suggested Hb target is ≥ 12 g/dl for females and ≥ 13 g/dl for males (Grade 2C). When the cause of anemia is unknown, nutritional factors, chronic renal insufficiency or chronic inflammatory disease should be considered (21). Erythropoiesis

Table 1

The adverse effects of common chemotherapeutic agents used and specific recommendations for the perioperative period

Category/Agents	Category common side effects	Side effects of particular agents	Actions/Specific precautions
Anthracycline antibiotics: - Doxorubicin - Daunorubicin	- Acute/chronic cardiac toxicity - QT-prolongation/TdP - SVT, ST-T changes, ↓ QRS voltage, bundle-brunch block, complete heart block, VT - Pericarditis, myocarditis - Myocardial depression with anesthetics even with normal resting cardiac function with risk of cardiomyopathy rises with increasing or cumulative dose	*Doxorubicin:* - In vitro: ↑ cytotoxicity with lidocaine/prilocaine - Cardiac: intraoperative cardiac arrest reported - Blood: acute myeloid leukemia - Pulmonary: fibrosis - Hepatic (rare) *Daunorubicin:* - QT-prolongation enhanced with isoflurane	- Careful with pts with pre-existing cardiac disease, elderly, or with previous myocardial irradiation (↑ risk) - Chest Xray (exclude cardiomegaly) - Consider cardiac U/S preoperatively - Careful with anesthetic-induced myocardiac depression (especially isoflurane) - Careful with QT-prolonging drugs
Topoisomerase inhibitors: - Etoposide	N/A	- Pulmonary: interstitial infiltrates, dyspnoea, respiratory failure - Stomatitis - Peripheral neuropathy (1%)	- Pulmonary toxicity may respond to steroids - Consider neuropathy when planning RA
Vinca alkaloids: - Vincristine	N/A	- Peripheral neuropathy: paresthesias, ↓ of deep tendon reflexes, motor dysfunction, gait disturbances - SIADH	- Consider neuropathy when planning RA - Check electrolyte levels
Taxanes: - Paclitaxel - Docetaxel	- Cardiac: asymptomatic bradycardia, severe bradyor tachyarrhythmias - Peripheral/autonomic neuropathy (50-70% at high doses), reversible sensory neuropathy (persistent paresthesias, burning, ↓ reflexes with high doses)	*Paclitaxel:* - Cardiac: VT	- Careful neurological examination preoperatively (consider neuropathy when RA is planned)
Platinum analogues: - Cisplatin (Platinum) - Carboplatin	N/A	*Cisplatin:* - Hearing impairment (40%) - Visual impairment - Encephalopathy, peripheral neuropathy (stocking/glove distribution, loss of deep tendon reflexes) - Nephrotoxicity (30-35%), wasting of Mg^{+2}, K^{+} - Cardiotoxicity (rare), extreme bradycardia, VT, QT-prolongation/TdP - Hepatic toxicity *Carboplatin:* - Neurotoxicity - Hepatic toxicity (↑ALP, AST, bilirubin) - Peripheral neuropathy - Mg^{++} loss	- Ensure adequate hydration + diuresis - Consider using aminoglycosides (nephrotoxicity accentuated) - Check electrolyte levels - Evaluate hepatic function - Careful with QT-prolonging drugs - Consider neuropathy when planning RA
Antimetabolites: - Methotrexate	N/A	- ↓ excretion with NSAIDs àacute renal failure - ↓antifolate activity with N_2O (especially within 6h after N_2O) - Acute encephalopathy-usually reversible (confusion, seizures, hemiparesis, coma) - Hepatic fibrosis, cirrhosis - Mucositis - Pulmonary: hypersensitivity pneumonitis, non-cardiogenic pulmonary oedema, fibrosis	- Avoid NSAIDs if possible - Avoid N_2O, administer leucovorin - Consider coagulopathy/neuraxial anesthesia - Dose reduction of drugs metabolised in the liver - Caution during intubation

Alkylating agents: - Ifosfamide - Cyclophosphamide	- Blood: acute myeloid leukemia - Cardiotoxicity: SVT, ST-changes	*Ifosfamide:* - Acute tubular necrosis, subclinical renal impairment (48%), hematuria (12%), chronic renal impairment (6%), hemorrhagic cystitis, - ↑ anticoagulant effect of coumarins - Encephalopathy, cerebellar dysfunction, hemiparesis, coma, extrapyramidal effects (0-10%) *Cyclophosphamide:* - Pseudocholinestare inhibitor properties lasting for 3-4 weeks - ↑ risk of death with halothane in mice - Cardiotoxicity (rare), acute pericarditis, hemorrhagic myocarditis - Hemorrhagic cystitis - Hepatotoxicity: diffuse hepatocellular damage, hepatomegaly, ascites, encephalopathy - SIADH - Pneumonitis ± fibrosis (<2%)	- Ensure adequate hydration + diuresis - Avoid NSAIDs - Careful with succinylcholine, dose reduction (for cyclophosphamide) - Check electrolyte levels
Actinomycines: - Dactinomycin	N/A	- Hypocalcemia - Mucositis - Hepatotoxicity	- Caution during intubation - Evaluate hepatic function, consider dose reduction of drugs metabolised in the liver
Newer agents: - Trabectedin (ET-743)	N/A	- Hepatotoxicity - Rhabdomyolysis - Fever, arthralgias	- Evaluate hepatic function, consider dose reduction of drugs metabolised in the liver - Check electrolyte levels

Percentages, when known, are included in parenthesis. N/A: not available/applicable information, RA: regional anesthesia, TdP: Torsades de Pointes, SVT: supraventricular tachycardia, VT: ventricular tachycardia, U/S: ultrasound, SIADH: syndrome of inappropriate antidiuretic hormone secretion, NSAIDs: Nonsteroidal anti-inflammatory drugs.

promoting agents could be helpful in patients without nutritional deficiencies (21). Nevertheless, the risk of deep venous thrombosis associated with erythrocyte stimulating agents such as epoetin alpha should be carefully weighed (22). Antithrombotic prophylaxis is suggested in patients who receive such agents and are scheduled for spine surgery (22). Erythrocyte stimulating agents should not be given in the absence of iron supplementation in cases of iron deficiency and the targeted Hb should not be higher than 14 g/dL (23).

Distress and depression may appear in 70% of cancer patients (12). Thus, premedication should be considered, tailored to individual needs.

Type of anesthesia and the role of peripheral nerve blocks

Both general and regional anesthesia can be used. All common general anesthetics and adjuvants can be administered according to patient's medical history. Epidural analgesia provides superior pain control and patient satisfaction compared with intravenous opioid patient controlled analgesia (PCA) (24). Moreover, neuraxial techniques have been considered to reduce intraoperative blood loss and deep venous thrombosis, although the latter has been questioned in recent meta-analyses considering the implementation of appropriate prophylactic anticoagulation (25).

Special considerations should be taken into account when epidural analgesia is planned for patients with spinal tumors. Spinal stenosis may reduce the compliance curve of the epidural space, thus affecting drug distribution or causing decreased clearance of drugs, resulting in high epidural pressures with continuous infusions. Spinal "coning" and paraplegia are associated with the presence of complete spinal block caused by a spinal tumor when lumbar puncture is attempted at the level or below the lesion (26, 27). Neuraxial techniques are relatively contraindicated in such cases (28-31). A retrospective study by Hollis et al analyzed neurological complications following cervical or lumbar puncture in patients with a complete block in myelogram due to several spinal masses concluding that lumbar puncture has an estimated risk of downward spinal coning of 14% (32). However, in the absence of complete spinal block, cesarean delivery under spinal anesthesia in a parturient with spinal metastasis from a soft tissue clear cell sarcoma and respiratory failure can be

preferable than general anesthesia (33). In any case, if a patient develops persistent paresthesia during catheter insertion or neurological deficit during infusion, drug injection should be discontinued. If symptoms continue, an MRI should be performed (26).

Peripheral nerve blocks, where applicable, are a valuable alternative or adjuvant to general or neuraxial anesthesia. They represent a safe anesthetic modality, since they are associated with minimal hemodynamic and respiratory changes, especially in sick patients. Prevention or treatment of phantom limb pain is an additional advantage (34, 35). Continuous catheter techniques provide excellent postoperative analgesia and minimize systemic opioid requirements (36). Moraes et al described a successful forequarter (interscapulothoracic) amputation for soft tissue sarcoma in a patient with severe coronary heart disease performed under an interscalene brachial plexus block supplemented with additional infiltration of the posterior thoracic lines of incision with 40 ml of local anesthetic and light sedation (37). In cases of pre-existing peripheral nerve lesion, due to mechanical compression or infiltration or damage caused by chemotherapy/radiotherapy, disturbances in axonal flow kinetics and in neurofilament architecture associated with peripheral nerve blockade may aggravate nerve function, a complication known as double crush phenomenon, the mechanism of which is not fully understood. Patients are susceptible to block prolongation and neurotoxicity (38). Peroneal nerve dysfunction was recently described in two patients with distal femur osteosarcoma who underwent preoperative chemotherapy (cisplatin, methotrexate, doxorubicin), followed by limb salvage surgery and postoperative 0.2% ropivacaine infusions via sciatic and femoral catheters (39). Electromyographic and nerve conduction studies showed axonal changes in the affected sciatic nerve and generalized subclinical nerve dysfunction in all extremities. Tourniquet inflation, extreme leg positioning, hypotension, hematoma and anesthetic technique may have played a role. The exact contribution of the double-crush risk has not been substantiated yet, thus it would not seem reasonable to withhold regional techniques unless further studies prove otherwise.

Finally, there is a growing body of evidence suggesting that anesthetic technique may influence cancer recurrence. Anesthetic drugs, pain, and opioids are all implicated in reduction of cellular immunity (40). Epidural anesthesia combined with general anesthesia may reduce the stress reaction and the effect of anesthetic drugs on the T lymphocyte subsets, contributing to the restoration of immune function in patients undergoing radical resection for knee osteosarcoma (41). Furthermore, local anesthetics exhibit a cytotoxic effect in vitro (42). Despite the abovementioned encouraging laboratory outcomes of regional anesthesia these are not confirmed by any strong clinical studies. A recent systematic review focusing on survival after orthopedic oncologic surgery concluded that there is a paucity of clinical evidence to support the theory that regional anesthesia could improve survival (43). Regional anesthesia, including peripheral nerve blocks, does reduce the stress response to surgery as well as opioid and volatile requirements, which are known to suppress cellular immunity, but whether this can be translated into long-term survival benefit remains to be elucidated (44). In any case, factors that negatively affect the immune system, such as patient anxiety, hypothermia, allogeneic blood transfusion, perioperative mal-nutrition should be minimized (40). Similarly, factors that reduce perioperative stress response and enhance immunity, i.e. adequate pain control, multimodal analgesia, neuraxial analgesia, should be implemented in clinical practice (40).

Intraoperative considerations

Invasive arterial blood pressure monitoring is advised in cases with anticipated blood loss or cardiovascular comorbidities. In high risk patients, including those with chemotherapy-induced cardiotoxity, cardiac output monitoring should be considered. Close heart rate monitoring is advised in patients who are on chemotherapy and receive granisetron, due to risk of bradycardia (45). Thromboelastography (TEG) and Rotation Thromboelastometry (ROTEM) can identify the reason of coagulopathy in major hemorrhage and should be used for goal-directed bleeding control (46). Adequate hydration is required to reduce the risk of hemorrhagic cystitis in patients who have been treated with ifosfamide (13).

Cemented procedures carry the risk of bone cement implantation syndrome (BCIS). High-risk patients are those with metastatic bone tumors and pathological fractures, pre-existing chronic obstructive pulmonary disease, pulmonary hypertension or cardiac comorbidity, high ASA scores, and those receiving diuretics or warfarin (47). End-tidal CO_2, arterial waveform, central venous pressure and transesophageal echocardiography provide valuable information. Transesophageal

Doppler can be helpful in early detection. High index of suspicion is required in cases of hypotension, desaturation and arrhythmias (47). Pulmonary vascular resistance may be increased and cardiac output reduced (47). There is no clear evidence that the anesthetic technique could prevent BCIS, but there are actions to decrease the severity of the adverse clinical outcome. Increased inspired oxygen concentration, avoidance of intravascular volume depletion and aggressive early management of hypotension and/or arrhythmias (41). Cementless stems are increasingly gaining acceptance in limb-salvage surgery and should be considered in high-risk patients. Pala et al in a retrospective study of 232 patients found that cementless stems resulted in higher survival rates than cemented stems in limb salvage operations (48).

Optimal patient positioning is important in facilitating surgical exposure. Specific care is required when patients are placed in prone position and operating time is prolonged, as in sacral tumor resections. Poor prone positioning has been associated with increased intraoperative hemorrhage, increased risk of blindness, nerve injury and skin breakdown (49). Position-related morbidity is more frequent in obese patients or procedures lasting more than 10 hours (49). The American Society of Anesthesiologists Task Force on perioperative blindness has recommended that in high-risk surgical procedures patient's head should be at a neutral forward position, at the level of the heart or slightly above it (50).

Postoperative care and analgesia

According to patient's clinical condition, comorbidities and blood loss, postoperative admission to a high dependency unit should be considered. In fact, surveillance of high-risk patients in a post-anesthesia care unit has been found to contribute to a reduction in mortality (51).

Acute postoperative pain management may be extremely challenging. Inadequate pain relief is associated with poor rehabilitation and development of chronic pain conditions, along with known complications such as hyperglycemia and immunosuppression. Multimodal analgesia is widely used. Among adjuvants, low dose ketamine produces an opioid sparing effect (52). A recent meta-analysis by Laskowski et al, including orthopedic limb and spinal surgery, has confirmed its benefit on acute pain management when given as bolus, infusion or in PCA, in terms of improved pain scores along with a decrease in opioid consumption and postoperative nausea/vomiting (53). Added to morphine PCA (1mg morphine plus 5mg ketamine per bolus dose) in musculoskeletal cancer patients, it reduces pain scores and morphine consumption without increasing the incidence of hallucinations. Furthermore, it aids physiotherapy which is mandatory for early rehabilitation and recovery (54). On the contrary, Hayes et al did not find a decrease in morphine consumption in lower limb amputation surgery. Even though there was a reduction in phantom pain at 6 months, no reduction in stump pain was noted at the same time (55).

Dexamethasone has been found to decrease oxycodone consumption in bone day surgery. However, more research is required before it can be implemented as an analgesic adjuvant after major orthopedic surgery (56). Intraoperative magnesium in doses of 50 mg/kg reduces opioid consumption and pain scores after major lumbar surgery, but there is a risk of prolongation of neuromuscular blockade (57). In spine surgery, the combination of magnesium with ketamine offers better pain relief than ketamine alone (58). Perioperative gabapentin and pregabalin have been studied extensively with positive results in some studies and conflicting in others (59-68). The inconsistency may be related to dose, timing and type of surgery (63, 65). Overall, they seem to reduce postoperative opioid consumption and chronic pain development in major musculoskeletal surgery (59, 60). There is also evidence that rapid recovery protocols can be applied in sarcoma cases without compromising surgical or oncological outcomes (69). In recent years intraoperative lidocaine infusion has been studied as part of multimodal analgesia. To date the effect of lidocaine administration in orthopedic malignant surgery has not been investigated. However, it offers no benefit in hip arthroplasty (70). In addition a recent Cochrane systematic review found no evidence of benefit in any surgical procedure apart from abdominal surgery (71). In lumbar microdiscectomy on the contrary it has been proven to reduce pain up during the first 24 hours postoperatively, but not at 48 hours (72). So, there is no robust evidence to support the use of lidocaine and more studies in orthopedic oncology surgery are needed in order to clarify its role in this setting. The clinical studies on postoperative care and analgesia are presented in Table 2.

Important perioperative considerations

Thromboembolic prophylaxis

Deep venous thrombosis (DVT) is a major issue in patients presenting for bone or soft tissue tumor

Table 2

Studies investigating postoperative care and analgesia in bone and soft tissue cancer surgery

Author [Reference]	Type of study (number of pts)	Type of surgery & aim of the study	Findings of the study
Sharrock et al. 1995[51]	Retrospective study (n=15519)	• Total hip or knee arthroplasty • Investigation of in-hospital mortality	• Significant decrease in mortality during 1987-91 (0.1%) versus 1981-85 (0.39%) • Possible role of hemodynamic periop monitoring and overnight stay in postanesthesia care unit
Deng et al. 2009[52]	RCT, double blinded (n=200)	• Surgery for lower limb fracture • Ketamine as analgesic adjuvant - Periop ketamine infusion 0.05-0.1 mg/kg/h	Ketamine was associated with • Reduced postop pain and remifentanil consumption • Increased patient satisfaction • No drug-related side effects
Kollender et al. 2008[54]	RCT, double blinded (n=57)	•Bone and soft tissue cancer surgery • Ketamine as analgesic adjuvant - Subanesthetic ketamine plus 2/3 the standard dose of morphine for postop IV PCA	The analgesic regimen resulted in • Lower pain scores and 60% morphine sparing effect • Faster discontinuation of PCA • Better early physical performance
Hayes et al. 2004[55]	RCT (n=45)	• Amputation above or below knee • Ketamine as analgesic adjuvant - 0.5 mg/kg IV followed by 0.5 mg/kg/h postop infusion - Postop PCA morphine IV	Ketamine did not reduce significantly • Morphine postop consumption • Intensity of post-amputation pain • Central sensitization
Mattila et al. 2010[56]	RCT (n=60, 50 analyzed)	• Osteotomy of the first metatarsal bone • Dexamethasone as analgesic adjuvant - Periop dexamethasone 9mg per os	Dexamethasone • Reduced postop oxycodone consumption
Levaux et al. 2003[57]	RCT (n=24)	• Major lumbar surgery • Magnesium sulphate as analgesic adjuvant - Intraop magnesium sulphate (50 mg/kg IV infusion)	Magnesium sulphate • Reduced postop pain and opioid consumption • Improved first night's sleep and patient satisfaction
Jabbour et al. 2014[58]	RCT, double blinded (n=50)	• Scoliosis repair surgery • Ketamine & magnesium as analgesic adjuvants - Intraop Ketamine IV 0.2 mg/kg & magnesium 50 mg/kg, followed by infusion of ketamine (0.15 mg/kg/h) & magnesium (8 mg/kg/h) - Multimodal postop analgesia/ morphine PCA	The combination of Ketamine/magnesium • Reduced post-operative morphine consumption • Improved sleep quality and patient satisfaction
Burke and Shorten. 2010[60]	RCT, double blinded (n=40)	• Lumbar discectomy • Periop administration of pregabalin as analgesic adjuvant	Pregabalin was associated with • Better acute pain tolerance postop • Less pain and disability at 3 months postop
Pandey et al. 2004[61]	RCT (n=56)	• Lumbar discoidectomy • Preop administration of gabapentin as analgesic adjuvant	Gabapentin was associated with • Less pain and fentanyl consumption postop
Pandey et al. 2005[62]	RCT, double-blinded (n=100)	• Lumbar discectomy • Testing the optimal preop dose of gabapentin as analgesic adjuvant	Gabapentin • Reduced postop pain and fentanyl consumption • The optimal dose was 600 mg
Radhakrishnan et al. 2005[63]	RCT, double-blinded (n=60)	• Lumbar laminectomy/discectomy • Preop administration of gabapentin as analgesic adjuvant - Gabapentin 400 mg X2 preop /PCA morphine postop	Gabapentin • Did not decrease postop morphine consumption or side effects
Turan et al. 2004[64]	RCT, double-blinded (n=50)	• Spinal surgery • Preop administration of gabapentin as analgesic adjuvant - Gabapentin 1200 mg preop/PCA morphine postop	Gabapentin was associated with • Less pain and morphine consumption postop • Less morphine-related side effects.
Montazeri et al. 2007[65]	RCT, double-blinded (n=70)	• Lower extremity orthopedic surgery • Preop administration of gabapentin as analgesic adjuvant - Gabapentin 300 mg preop/morphine on demand postop	Gabapentin was associated with • Less pain and morphine consumption postop
Clarke et al. 2009[66]	RCT, double-blinded (n=126)	• Total hip arthroplasty • Gabapentin as analgesic adjuvant - Gabapentin 600 mg preop or postop (single dose) - Spinal anesthesia - Multimodal postop analgesia	Gabapentin • Did not decrease postop morphine requirements or in-hospital pain or pain at 6 months
Buvanendran et al. 2010[67]	RCT, double-blinded (n=240, 228 analyzed)	• Total knee arthroplasty • Periop pregabalin as adjuvant for chronic/ acute postop pain - Pregabalin 300 mg preop / continuation for 14 days	Pregabalin was associated with • Lower incidence of neuropathic pain at 3 and 6 months • Less opioid consumption during hospitalization • More early postop sedation/confusion
Sheen et al. 2008[68]	RCT, double-blinded (n=86)	• Lower limb surgery • Gabapentin for prevention of intrathecal morphine pruritus - Gabapentin 1200 mg preop - Spinal anesthesia (bupivacaine plus morphine)	Gabapentin • Reduced the spinal morphine-induced pruritus

Pts: patients, Periop: perioperatively, Postop: postoperatively, Intraop: intraoperatively, RCT: Randomized controlled trial, PCA: Patient Controlled Analgesia

resection. Cancer itself carries a fourfold increase in the risk of thrombosis, while major orthopedic surgery is also independently associated with a high risk of DVT (73, 74). Bone tumors (compared to soft tissue sarcoma) and prosthetic reconstruction represent additional risk factors (73, 74). The reported incidence of pulmonary embolism (PE) in cancer patients undergoing musculoskeletal tumor surgery ranges between 0.6 and 11% in different studies with heterogeneity in group sizes, study subjects, diagnosis, follow-up and prophylactic measures (74). Rates of PE in orthopedic tumor patients when both mechanical prophylaxis and anticoagulation are applied are estimated to be between 0.6 and 1% (75, 76).

Pharmacologic anticoagulation in terms of low-molecular-weight heparin is a standard approach, but may not always be effective, as cancer patients are at increased risk of DVT despite such therapy. It also carries the drawback of worsening perioperative bleeding. Mechanical prophylaxis should be applied when the site of surgery allows it. In major orthopedic surgery, a combination of pharmacoprophylaxis, mechanical compression and early mobilization reduces the risk of DVT (77).

Inferior vena cava (IVC) filters constitute an effective means of PE prophylaxis and there are studies supporting its use in musculoskeletal cancer patients (73, 78). Advantages include no interference with bleeding control, easy insertion and long-term protection. Tuy et al studied retrospectively 81 patients with lower extremity or pelvic malignancy and preoperative placement of IVC filter (73). Mechanical prophylaxis (both antiembolism stockings and sequential compression devices) was also applied, while pharmacological anticoagulation was omitted. In a minimum follow up period of 3 months, DVT rates were 21% and symptomatic PE 2%, with no fatality.

Management of perioperative hemorrhage

Autologous transfusion in the form of predonation and acute normovolemic hemodilution may be used whenever possible. Antifibrinolytic agents have also been studied (79). Zufferey et al found that aprotinin and tranexamic acid, but not ε-aminocaproic acid, reduced blood loss and transfusion requirements, without increasing thromboembolic events. Nevertheless, there was no conclusion on agents' overall safety profile (80). Tranexamic acid has been found to reduce blood loss in hip surgery, but not significantly in cemented knee replacement under tourniquet and meticulous surgical hemostasis before wound closure (81, 82). Amar et al compared the administration of aprotinin, tranexamic acid and placebo in major musculoskeletal surgery for cancer, primary or metastatic, and found no difference between groups regarding blood loss (83).

Blood salvage constitutes an effective method of blood conservation. It reduces allogeneic blood transfusion in revision hip replacement, but not in operative treatment of acetabular fractures (84). In cancer surgery, intraoperative cell salvage has been traditionally avoided due to its risk of promoting tumor dissemination by infusing cancer cells back to the patient. Nevertheless, this risk is mainly theoretical and not proven. For radical prostatectomy and cystectomy it has been demonstrated that intraoperative cell salvage reduces blood transfusion without affecting negatively the survival rates. In 2008, NICE guidelines endorsed cell salvage in the abovementioned procedures (85). Leucocyte depletion filters (LDF) should be used in malignancies, as they remove tumor cells (84). Catling et al conducted an observational study on the ability of LDF to remove tumor cells in 50 patients undergoing major gynecologic oncology surgery (86). Tumor cells were found in 4% of preoperative samples, in 68% of cell saver reservoirs before processing, in 62% after processing, while no tumor cells were found after blood passage through LDF. Another recent study recruited 24 patients undergoing metastatic spine surgery in order to evaluate the LDF (87). No viable malignant cells were detected after passage through the filters. A systematic review of Kumar et al also found that intraoperative cell salvage with LDF is not associated with higher risk of tumor dissemination or metastasis (88). Concluding, there is no reason not to support its use in metastatic musculoskeletal tumor surgery, however, currently no recommendations for its use in orthopedic tumor resections exist.

Specific concerns/procedures and relevant implications

Management of major soft tissue defects

Resection of large musculoskeletal tumors is often accompanied by removal of large parts of bone and soft tissue (10). Primary closure of subsequent soft tissue defects may not be possible rendering patients at high risk for wound complications (89). Preoperative radiation and lower extremity location, along with smoking, diabetes mellitus and vascular disease represent additional risks for

wound complications (90, 91). Special anesthetic considerations are required in free tissue transfer. Invasive blood pressure monitoring enables safe control of tissue perfusion pressure, while temperature monitoring is required to avoid hypothermia. Active warming should start before anesthesia induction and continue during and after operation. A hematocrit of about 30% seems to offer the best balance between blood viscosity and oxygen transfer to the flap. Careful fluid management helps to maintain hemodynamic stability while avoiding flap edema. Normocarbia must be ensured, since hypocarbia increases peripheral vascular resistance and decreases cardiac output, while hypercarbia induces sympathetic stimulation and reduces erythrocyte flexibility. Regional anesthetic techniques are beneficial because of the sympathetic blockade and subsequent vasodilation. Among general anesthetics, there is *no* clear *advantage* of one *over the others, according to existing evidence* (92).

Tumor embolization/ Percutaneous musculoskeletal tumor management

Embolization is used as the main treatment or in adjunction to surgical excision. One of its main indications is the avoidance of excessive blood loss during surgery of highly vascularized lesions. Older studies based on small case series of preoperative embolisation of spinal tumors proving effectiveness in reducing perioperative blood loss have been questioned lately (93). In a retrospective, single-institution cohort study of 104 patients with spinal tumors, no correlation between degree of embolization and blood loss and/or blood transfusion was found (94). Tumor volume, surgical approach, and invasiveness of the spinal surgery have been suggested as significant factors affecting blood loss (95). Complications of embolisation may be rare but severe, namely cord ischemia and paraplegia or even aortic dissection (96). Other indications of tumor embolisation such as pain management, increase in sensitivity to chemotherapy or radiation therapy and management of hypercalcemia are also under consideration. It can be performed under general or local anesthesia with conscious sedation. The latter allows for neurological monitoring during procedures in high risk areas. On the other hand, general anesthesia can help in avoiding involuntary movement during procedures in critical areas. Both anesthetic methods have been used safely (97). Thus, choice should be based on patient's medical status and tumor location.

Various percutaneous techniques are used for pain management and strengthening of pathological bone (i.e cementoplasty), or tumor size reduction (i.e cryoablation). Percutaneous cementoplasty can be performed under general anesthesia or light sedation combined with local anesthetic infiltration, depending on tumor location and patient's comorbidities and degree of cooperation (98). Percutaneous alcohol ablation is usually performed under local anesthesia plus neuroleptoanalgesia, since intra-tumoral injection of ethanol may be quite painful. Laser photocoagulation commonly used in osteoid osteomas, which are very painful benign tumors, usually requires adequate general or regional anesthesia (99). Microwave ablation, a form of thermal ablation that is generally used for the management of solid tumors in patients who are not suitable candidates for surgical excision, has recently been used in musculoskeletal tumors with promising results. Nitrous oxide inhalation plus local anesthesia seems adequate (100). Cryoablation is usually performed under mild sedation or just local anesthesia since it possesses intrinsic anesthetic properties, in contrast to radiofrequency ablation that is rather painful requiring general anesthesia (101). Motor evoked potentials are a useful tool for minimising the risk of motor injury during perineural treatment. Persistent intraoperative motor evoked potential decreases are correlated with postoperative motor deficits (102). Recently dexmedetomidine use has been introduced. A report describes its use in the removal of a vertebral metastatic tumor via a single port endoscopic approach in an 82 year-old patient in prone position. In this case a loading dose of 0.5 μg/kg followed by 0.3-0.5 μg/kg/h of dexmedetomidine plus fentanyl 50 μg were used (103).

Conclusions

Perioperative management of patients with musculoskeletal tumors is quite challenging due to the increasing complexity of surgical techniques and perioperative treatment modalities. The characteristics of the tumor, the chemotherapeutic agents used, as well other perioperative risks may have various implications in anesthetic practice.

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