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QUESTION 4: What should be the time delay between preoperative chemo/radiotherapy and a surgical tumor resection in order to minimize incidence of surgical site infection/ periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Unknown. There is no data that supports the best time delay between preoperative chemo/radiotherapy and a surgical tumor resection to minimize the incidence of SSI/PJI. There are multiple intrinsic factors of each patient that can determine the best time to implant an endoprosthesis after a neoadjuvant treatment. Although no significance was seen between preoperative radiotherapy and surgical timing on wound complications (WC), trends suggest rates are lower if surgery is performed between 3 and 6 weeks following radiotherapy.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

SSIs, PJIS and WCs can occur postoperatively with respect to musculoskeletal/orthopaedic related surgeries. The risk of these infections is more common when these surgeries are related to musculoskeletal tumor resections following established multimodal therapies of preoperative chemotherapy and/or radiotherapy [1,2]. SSIs are defined as infections occurring at the operative site that develop within 30 days of non-implant operation or 1 year in the case of implant (artificial material) based operations [3]. The incidence of SSIs following orthopaedic operations is 1–3% [4]. The incidence is expected to be much higher following surgery in malignant musculoskeletal tumors due to many patients' requiring preoperative/postoperative chemotherapy and/or radiotherapy. PJI after joint replacement surgery has been reported to occur in 1.55–2.5% of cases [5–7]. As with SSIs the incidence would be expected to be higher following tumor surgery. Wound complications rates have been shown to be higher in those receiving preoperative radiotherapy [6,8–10].

With respect to the timing of surgery after preoperative radiotherapy and/or chemotherapy, there is no established optimal timeframe for clinical practice. Decisions to date are made by clinician-team opinion. The effect of different timeframes on the development of SSI, PJI and WC rates in this group has not been extensively reviewed. We know that radiation impairs wound tissue repair though several mechanisms [11]. Ionizing radiation can damage fibroblasts leading to slow growth [12,13], dermal atrophy, necrosis and ultimately reduced wound strength [14–16]. As a result, in the initial period following radiotherapy, surgery is avoided and four weeks is thought to be required to allow for repopulation of normal tissues [17]. Acute systemic effects of chemotherapy are also well documented, including toxicity and immunosuppression. However, there is still no established timeframe with respect to when to surgically resect tumors post chemotherapy and this is guided by clinical assessment and clinician choice.

All seven included studies were retrospective case studies, four were single-center studies, while the other three were not specified. The total sample number of all seven studies combined was n = 1,585; sample sizes ranged from 18-798. Preoperative radiotherapy was used in five of the studies, preoperative chemotherapy in three.

SSI was statistically significant secondary to preoperative radiotherapy alone in three studies [19,21,23] and secondary to preoperative chemotherapy in two studies [21,22]. No statistical significance with respect to SSI and preoperative chemotherapy in one study [18]. The remaining two studies did not statistically assess SSI as an outcome measure [17,20]. Sugita et al., 2015, intended to study the effect of timing between radiotherapy and surgery on SSI; however, this was abandoned due to factors varying widely between cases [19].

None of the six included studies assess PJI as an outcome measure. There was no mention of PJIs being included in any other groups as a complication. Furthermore, no data on the effect of timing between radiotherapy and surgery on PJI was sourced.

One study showed statistical significance between neoadjuvant radiotherapy and postoperative infection, p = 0.008. This study did not classify specifically the type or location of these infections [23].

In terms of WC two of the studies assessed their association with preoperative treatment. Both studies looked at the effect of preoperative radiotherapy. Keam et al. (n = 165) investigated the effect of preoperative radiotherapy on WCs and no statistical difference was evident with univariate analysis (p = 0.11) [20]. This study also looked at the timing effect of < 30 (n – not specified) days and ≥ 30 days (n – not specified) between radiotherapy and surgery on WC rates. There was no statistical significance between these two timeframes (p = 0.59) [20]. Griffin et al., investigated the dichotomous effect of the time intervals of 3, 4, 5 and 6 between preoperative radiotherapy and surgery. The rate of wound complications was the primary outcome measure. When comparing ≤ 3 and > 3 weeks, WC rates were 15/39 (38%) and 227/759 (30%) respectively, p = 0.3. Comparing ≤ 4 and > 4 weeks, WC rates were 39/129 (30%) and 203/669 (30%) respectively, p = 1. Comparing ≤ 5 and 5 weeks, WC rates were 88/295 (30%) and 154/503 (31%) respectively, p = 0.8. Comparing ≤ 6 and 6 weeks, WC rates were 133/479 (28%) and 109/322 (34%) respectively, p = 0.08. At time points < 3 and ≥ 6 weeks, it is evident that

TABLE 1. Data extraction from included studies

Author	Study Type	Neoadjuvant Treatment	Time Between Treatment and Surgery	n	Postoperative Outcome
Miwa et al., 2017 [18]	Single-centre Retrospective	Chemotherapy	Not specified	108	Deep SSI 16/108 significant with univariate analysis ($p < 0.001$), not significant in multivariate analysis ($p = 0.156$)
Sugita et al., 2015 [19]	Non-specified Retrospective	Radiotherapy	Intention to analysis effect of timing *Abandoned	41	SSI 27/41 significant with univariate analysis ($p = 0.03$)
Griffin et al., 2015 [17]	Non-specified Retrospective	Radiotherapy	≤ 3, > 3 weeks ≤ 4, > 4 weeks ≤ 5, > 5 weeks ≤ 6, > 6 weeks	39, 759 129, 669 295, 503 476, 322 Total n = 798	WC 15/39 (38%), 227/759 (30%), $p = 0.3$ WC 39/129 (30%), 203/669 (30%), $p = 1$ WC 88/295(30%), 154/503 (31%), $p = 0.8$ WC 133/479 (28%), 109/322 (34%), $p = 0.08$ Overall WC 186/798 (23.3%) incidence SSI 56/798 (7%) incidence, *effect of time not studied
Keam et al., 2014 [20]	Single-center Retrospective	Radiotherapy	> 30 days ≤ 30 days	165	No difference between effect of preoperative radiotherapy > 30 and ≤ 30 days from surgery on wound complications ($p = 0.59$) No significant effect on WC with univariate analysis ($p = 0.11$)
Gradl et al., 2014 [21]	Single-centrer Retrospective	Radiotherapy Chemotherapy	Immediate Not specified	262 137 Total n = 399	SSI 50/153, significant with bivariate analysis ($p < 0.0001$) SSI 22/153, significant with bivariate analysis ($p = 0.02$)
Nagano et al., 2014 [22]	Single-center Retrospective	Chemotherapy	Not specified	18	SSI 6/18, significant with bivariate analysis ($p = 0.03$)
Behnke et al., 2014 [23]	Non-specified Retrospective	Radiotherapy	Not specified	56	Postoperative infection (Location/type not specified) in those with radiotherapy 14/56 (25%) when compared to those without 37/340 (11%), statistically significant, $p = 0.008$

there is a higher rate of WC (34-38%) when compared to 3-6 weeks (28-31%); however, statistically there is no difference between time points [17]. This trend, although not significant, may support the general avoidance of aiming for surgery too early or too late based on radiation induced local changes to tissue and skin. A large multi-center study may show more of an effect at these timeframes. This trend may be considered applicable to SSI/PJIs due to WC risk factors being theoretically close in nature to infection risk, particularly the local and systemic toxicities and effects of radiotherapy and chemotherapy respectively.

We identified seven relevant articles assessing the effect of preoperative treatment on SSI, PJI and WC with respect to musculoskeletal tumour resection. Results are highly variable between the studies and overall there is limited evidence of significance in results. SSI rates were significantly increased in 3/3 (100%) of studies that looked at preoperative radiotherapy and 2/3 (67%) of the studies that looked at preoperative chemotherapy. These are single center/non-specified studies; to further delineate results, larger multi-centre studies in the future are warranted. No effect on timing of preoperative treatment and surgery was observed with respect to SSI rates. Given that there is conflicting evidence between the effect of preoperative tumour treatment and SSI development, investigation into the effect of timing becomes difficult. However, as some studies have established positive association and the near future possibility of larger multi-center study results coming to fruition, it will be now be imperative to also investigate and study the effects of surgical timing post radio/chemotherapy on rates of SSI. No studies assessed periprosthetic joint infection specifically as an outcome. This may be due to PJI presenting as a rare outcome secondary to surgical tumour resection. Also, these infections may be included in another complication section of such studies. None of the studies included in this review have mentioned this as an observed complication. Therefore, more investigation and study is needed with respect to understanding the role of preoperative tumour management and surgical timing on the rates PJI.

In summary, there is strong evidence supporting the association between preoperative radiotherapy/chemotherapy and postoperative SSIs. There is no data on the association of preoperative treatment with respect to PJI rates. One study showed no association between preoperative radiotherapy and WC. There were two studies showing no significant difference between surgical timing post radiotherapy/chemotherapy with respect to wound complications; however, there was a trend towards higher wound complications rates in ≤ 3 weeks and > 6 weeks. More large-scale, well-designed

multi-center studies are required to more accurately assess the effect of timing between preoperative radiotherapy/chemotherapy and surgery on the rate of postoperative SSIs, PJIs and WCs.

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QUESTION 5: What strategies should be implemented to minimize the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients who have received chemotherapy or radiation therapy and are undergoing endoprosthetic reconstruction?

RECOMMENDATION: We believe patients who have received either chemotherapy or radiotherapy prior to endoprosthetic reconstruction should undergo extensive medical optimization. Consideration may also be given to the use of antimicrobial coated implants, extended (>24 h) and augmented postoperative antibiotic prophylaxis consisting of a first-generation cephalosporin and an aminoglycoside and/or vancomycin, as well as use of enhanced soft tissue reconstruction techniques. Surgery should also be expeditious in these patients minimizing dissection of soft tissues with gentle handling.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Patients with neoplasia undergoing endoprosthetic reconstruction are at an increased risk of SSI/PJI. The chemotherapy-induced immunosuppression, the poor soft-tissue conditions due to radiotherapy, the length and complexity of the tumor resection and megaprosthetic reconstruction and the difficulty of achieving soft tissue coverage are some of the reasons that explain the very high rate of infection in these patients compared to patients undergoing conventional arthroplasty [1–5].

As these patients are at high risk of SSI and/or PJI, any measure proven to be effective against infection should be implemented. Several organizations have proposed evidence-based guidelines for the prevention of surgical site infections. These strategies, together with additional measures, should be implemented in these patients. We provide examples of some of the measures that may be used to minimize the risk of SSI/PJI in patients undergoing oncologic endoprosthetic joint reconstruction, particularly in patients who have received chemotherapy and/or irradiation treatment. These measures include:

- Preoperative measures [6–9]: Correction of hyperglycemia, treatment of anemia, treatment of malnutrition, smoking cessation, decolonization of *Staphylococcus aureus* (including methicillin-resistant *S. aureus* (MRSA)), skin cleansing with chlorhexidine or other antiseptic agents prior to surgery and numerous other preoperative measures that are discussed elsewhere in the consensus document should be considered.