Timing of surgery and radiotherapy in the management of metastatic spine disease: A systematic review

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Abstract. The last decade has witnessed a dramatic change in management of metastatic spine disease, with an increased role for surgery and emerging use of stereotactic radiotherapy, often in combination. Patients may be treated with radiotherapy followed by surgery, or have surgery and then adjuvant radiotherapy. In both cases, the surgeon and oncologist need to select the optimal timing for surgery and radiotherapy to minimize wound complications while obtaining maximum oncolytic effects. The purpose of this review was to determine the optimal timing of surgery and radiotherapy in patients surgically treated for spinal metastases. A systematic review utilizing Medline, Embase, Paper First, Web of Science, Google Scholar, and the Cochrane Database of Systematic Reviews was performed. References were screened to further identify relevant studies and basic science literature reviewed. A total of 46 reports discussing the timing of surgery after radiotherapy, describing experience in 5836 patients, were identified. Only one retrospective study addressed the research question and suggested that surgery within seven days of radiation increases the rate of postoperative wound complications. Timing of adjuvant radiotherapy following surgery was addressed in 51 reports describing 7090 patients. None of the studies specifically answered the research question. The time interval between radiotherapy and surgery was reported as 5-21 days in nine studies. Based on this systematic review together with the understanding of general principles of wound healing and effects of radiation on wound healing, the optimal radiotherapy-surgery/surgery-radiotherapy time interval should be at least one week to minimize wound complications.

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Contents

1. Introduction

Radiotherapy has traditionally been the mainstay of treatment for metastatic disease of the spine. Surgical indications were limited to neurologic deterioration during radiation and failure of radiation therapy, with a limited recognition of issues related to spinal instability. With advancements in biomaterials, spinal biomechanics, and imaging, along with innovations in surgical techniques, came an appreciation for spinal instability as a valid indication for surgical stabilization. Recently, the understanding that radiotherapy and surgery should often be combined in the management of both primary and metastatic tumors of the spine has reached maturity. This is especially true in the treatment of spine metastases, where several landmark studies demonstrated the benefit and cost effectiveness of surgery plus radiation vs. radiation alone (1-3). There are, however, potential adverse events associated with radiation delivered in close proximity to surgery, especially complications related to wound healing (4-6).

The approach to metastatic disease of the spine is undergoing a paradigm shift as a result of new technology in both the medical and surgical domains, thus the spine surgeon and radiation oncologist often encounter two different clinical scenarios. In the first scenario, a patient with spinal metastases has been treated with radiotherapy and then presents with mechanical back pain, progression of deformity, or neurological deterioration; surgical treatment for decompression and stabilization is thus indicated. In the second scenario, a patient who has had surgical treatment for metastatic cord compression subsequently requires radiotherapy. In the first scenario, the surgeon and oncologist need to decide the best timing for surgery in relation to previous radiotherapy, and in the second case the timing for radiation in relation to previous surgery is the issue. Although clinicians are asking these questions on a daily basis, the literature fails to provide clear guidelines, and in many cases treatment is given based on personal experience and educated hunches.

The objective of this study was to perform a systematic review of the literature relating to the optimal timing for surgery in previously irradiated patients, and for radiotherapy in previously operated patients, with consideration of wound healing complications. The advantages of a systematic review include transparency in the methodology, allowing readers to determine for themselves the acceptability of the process, and the reduction of bias and random error that are inherent to some case series and narrative reviews. A systematic review can thus be an important tool for reaching conclusions from literature that may prove difficult to interpret on a case-by-case basis.

2. Collection of the clinical data

Inclusion criteria. Inclusion criteria included: i) a population of patients with primary malignancy or metastatic disease of the spine and a minimum age of 18 years, and ii) intervention of spine surgery through a posterior approach, preceded or followed by radiotherapy. In studies meeting inclusion criteria, we extracted data regarding postoperative wound complication-wound infection, wound breakdown, and delayed wound healing. Articles not meeting the inclusion criteria were excluded from the review.

Literature search to identify primary studies. A comprehensive literature search was performed to locate relevant potential studies. Electronic database searches of Medline (1966-November 2007) and Embase (1980-November 2007) were performed using both medical subject headings (MeSH) and text word searching (Table I); Papers First, Web of Science, Google Scholar, and the Cochrane Database of Systematic Reviews were searched using text words. The major review articles were identified, and their reference lists were manually searched for additional citations. Experts in the field were sought and questioned as to possible additional references.

Study selection. Two independent reviewers (E.I. and C.F.) used a standardized study selection worksheet to evaluate the eligibility of each study. The reviewers were blinded to author, institution, and journal of publication. Articles were excluded based on abstract review if both reviewers independently determined that inclusion criteria were not met. Otherwise, all the remaining studies were assessed using the complete reports. Any disagreements between observers were resolved through discussion.

Table I. Search criteria.

1	Spine or spinal
2	Radiotherapy or radiation or irradiation
3	Surgery or laminectomy or vertebrectomy
4	Wound or complication or infection or breakdown or dehiscence
5	Cancer or neoplasm
6	1 and 2 and 3 and 4 and 5

General literature search. Because of the paucity of literature discussing the optimal timing of surgical and radiotherapy procedures in relation to wound healing for patients with primary and secondary spine tumors, we used the general medical literature and the literature on physiology of radiation and wound healing to provide necessary background to better answer the questions. A comprehensive search in the general clinical literature was performed, to identify randomized controlled studies and prospective case series that were designed specifically to answer our research questions in different medical disciplines.

3. Evaluation of the data

A total of 55 studies were identified in the electronic search. Fourteen were classified as possible for inclusion, but only five fully satisfied the two inclusion criteria (7-11). An additional 61 studies that met inclusion criteria were identified by a bibliography search.

Timing of surgery after radiotherapy. A total of 46 studies that met inclusion criteria, describing 5836 patients who underwent surgery after radiotherapy were identified (Table II). These studies were either surgical case series including some patients who had preoperative radiotherapy, or series describing patients managed primarily with radiation who needed continued treatment with surgery. Only one retrospective study was designed to address the question of timing of radiotherapy and postoperative complications (7). Six studies mentioned the time interval between radiotherapy and subsequent surgery (2,7,12-15).

Eight studies included analysis of the association between preoperative radiotherapy and postoperative complication rates (9,14-20). The relationship was significant in four studies, but did not reach statistical significance in four others. From 15 studies we were able to extract information on 309 previously irradiated patients that were treated surgically, with wound complication rates of 11-50% (2,7,8,10,14,21-30).

Only three studies included information on the timing of surgery after radiotherapy, and also provided enough information on wound-related complication rates. Ghogawala *et al* (7) found that patients who underwent surgery after radiotherapy had a 32% risk of wound-related complications compared with 12% for those who underwent surgery as the

Table II. Timing of surgery after radiotherapy.

Refs.	Description	Level of evidence (in relation to the primary question)	No. of patients meeting inclusion criteria	Treatment	Results	Conclusion
Ghogawala *et al* (7)	Retrospective	Level III	28	One-stage posterolateral decompression-stabilization	-9 patients suffered wound-related complications -46% complication rate if surgery was performed within 7 days of radiotherapy vs. 20% if surgery was performed more than a week after radiotherapy vs. 12% if radiotherapy was administered after surgery	Spinal radiation before surgical decompression for metastatic spinal cord compression was associated with a significantly higher major wound complication rate.
Helweg-Larsen *et al* (13)	Prospective	Level III	5	Laminectomy within 2 weeks of radiotherapy due to deterioration	-Postoperative course was not reported	Problem: small series.
Street *et al* (14)	Prospective cohort study	Level III	14	-Posterolateral vertebrectomy and fusion -All patients were operated on more than a week after completing radiotherapy	-3 patients suffered wound-related complications	Preoperative radiotherapy did not raise the rate of wound-related complications. Problem: radiotherapy-surgery time interval was greater than a week.
Fourney *et al* (16)	Retrospective	Level III	43	Surgery through a posterior or combined anterior-posterior approach	-Timing of radiotherapy in relation to surgery was not specified	Preoperative radiotherapy was significantly related to postoperative complications (p=0.02).
Wang *et al* (15)	Retrospective review of prospectively maintained database	Level III	84	Posterolateral transpedicular vertebrectomy with circumferential fusion	-Median time to failure of radiotherapy was 4.2 months (range 0.1-64.4 months) -Only 6 patients were operated within a week of radiotherapy	No association was found between preoperative radiotherapy and postoperative wound infection (p=0.21). Preoperative radiotherapy within 6 weeks prior to surgery did not increase the infection rate (p=0.29). Problem: radiotherapy-surgery time interval was greater than a week for most patients.

Table II. Continued

Refs.	Description	Level of evidence (in relation to the primary question)	No. of patients meeting inclusion criteria	Treatment	Results	Conclusion
Holman *et al* (17)	Retrospective	Level III	139	-46 patients were previously irradiated -85 were operated through a posterior or combined anterior-posterior approach		Preoperative radiotherapy was not significantly related to postoperative complications (p=0.17). Problem: association between preoperative radiotherapy, the specific surgical approach and wound complications was not examined. The issue of timing was not specified.
McPhee *et al* (9)	Retrospective	Level III	75 procedures on 53 patients	-52 were operated through a posterior approach -42 patients had perioperative radiotherapy (within a month prior to or a month after surgery)	-10 patients suffered wound infection	Perioperative radiotherapy was not significantly related to postoperative wound-related complications. Problem: perioperative radiotherapy and not preoperative radiotherapy was investigated as a risk factor for wound complications.
Sundaresan *et al* (18)	Retrospective	Level III	80	-32 were operated through an anterior approach -8 through a posterior approach -40 through a combined anterior-posterior approach -40 patients had preoperative radiotherapy	-10 patients suffered wound complications	Preoperative radiotherapy was significantly related to postoperative complications (p=0.03). Problem: association between preoperative radiotherapy, the specific surgical approach and wound complications was not examined. The issue of timing was not specified.
Sundaresan *et al* (19)	Retrospective	Level III	110	-47 were previously irradiated -59 were operated through a posterior or combined anterior-posterior approach	-40% (4/10) of the patients that were operated due to disease progression while on radiotherapy suffered complications	Complications were significantly more frequent in patients that had preoperative radiotherapy (p<0.001). Problem: association between preoperative radiotherapy, the specific surgical approach and wound complications was not examined.
Wise *et al* (20)	Retrospective	Level II	80	-Patients underwent 88 procedures, 48 through a posterior approach -41 patients had preoperative radiotherapy	-8 patients, who had all had preoperative radiotherapy, suffered wound infection, 7 of them in a posterior approach wound	Preoperative radiotherapy was significantly related to postoperative complications. Problem: when the results were analyzed according to the surgical approach, the number of patients in each group was too small to draw statistically significant conclusions.

Table II. Continued

Refs.	Description	Level of evidence (in relation to the primary question)	No. of patients meeting inclusion criteria	Treatment	Results	Conclusion
Akeyson *et al* (21)	Retrospective	Level III	20	Posterolateral vertebrectomy with circumferential fusion	-3 patients suffered wound dehiscence -4 had a persistent CSF leak	Problem: not specified whether the patients that had complications were from the preoperative radiotherapy group.
Harrington *et al* (22)	Not specified	Level III	6	Posterior augmentation for vertebrectomy through an anterior approach	-3 patients suffered wound dehiscence and deep infection	Problem: the issue of timing was not specified.
Heller *et al* (23)	Retrospective	Level III	22	Posterolateral decompression and Luque instrumentation	-6 patients suffered wound dehiscence -1 suffered wound infection -32 vs. 9% suffered wound complications in the previously irradiated vs. *de novo* surgery	Problem: the issue of timing was not specified.
Johnston *et al* (8)	Prospective	Level III	14	Posterolateral decompression and circumferential fusion	-5 patients suffered wound infection and dehiscence. -36% vs. 0 suffered wound complications in the previously irradiated vs. *de novo* surgery	Problem: the issue of timing was not specified.
Marshal *et al* (25)	Not specified	Level III	17	Decompressive laminectomy	-1 patient suffered persistent CSF leak	Problem: small sample size; timing not specified.
McLain *et al* (26)	Prospective	Level III	4	Tumor resection and fixation with VSP plate	-2 patients suffered wound infection	Problem: small sample size; timing not specified.
Overby *et al* (27)	Not specified	Level III	9	Tumor resection and posterior fixation with VSP plate	-2 patients suffered wound complications	Problem: small sample size; timing not specified.

Table II. Continued

Refs.	Description	Level of evidence (in relation to the primary question)	No. of patients meeting inclusion criteria	Treatment	Results	Conclusion
Pascal-Moussellard *et al* (10)	Retrospective	Level III	145	-125 patients were previously irradiated -113 were operated through a posterior or a combined anterior-posterior approach	-15 previously irradiated patients suffered wound complications -12 vs. 1.1% suffered wound complications in the previously irradiated vs. *de novo* surgery	Complications were significantly more frequent in patients that had preoperative radiotherapy. Problem: association between preoperative radiotherapy, the specific surgical approach and wound complications was not examined.
Sundaresan *et al* (29)	Not specified	Level III	14	Decompressive laminectomy	-4 patients suffered wound complications	Problem: the issue of timing was not specified.
Shaw *et al* (28)	Not specified	Level III	6	One-stage postero-lateral decompression-stabilization procedure	-No patients suffered wound-related complications	Problem: small sample size.

initial therapy. These authors also found that the wound complication rose to 46% when surgery was performed within seven days of radiotherapy, compared with 20% if the radiation surgery interval was longer then a week. Patchell *et al* (2) also showed a 30% wound-related complication rate in patients who failed radiotherapy and required rapid surgical inter-vention. Most of these surgeries occurred within a week of radiation. Interestingly, Street *et al* (14) found that approxi-mately 20% of patients who where treated with posterolateral vertebrectomy, with or without preoperative radiotherapy, experienced major wound-related complications. Surgery was never performed within the first week after radiotherapy in patients in the Street series.

Timing of radiotherapy after surgery. A total of 51 studies that met inclusion criteria, describing 7090 patients who underwent radiotherapy after surgery, were identified (Table III). None of these studies was designed to specifically address the question of timing. To address the question of the timing of radiotherapy following surgery, we extracted information from numerous case series describing, in part, patients who were treated with surgery followed with radiotherapy for metastatic spinal disease. Nine studies reported the surgery-radiation time interval to be 5 to 21 days (2,31-38). One study found no significant association between postoperative radiotherapy and complications (20).

Only eight studies encompassing 122 patients treated with surgery and postoperative radiotherapy presented complete data. Among these, only nine patients (7.4%) suffered post-operative wound-related complications. Five studies reported no complications (7,21,24,28-30,35,38). Among these eight, only studies by Young *et al* (38) and Laohacharoensombat *et al* (35) reported the surgery-radiotherapy interval, which was 7 and 14 days, respectively.

4. Discussion and conclusions

The question of when to operate on or irradiate a patient is encountered frequently in spine oncology. Despite advances in radiation oncology (e.g. radiosurgery) and innovative minimally invasive surgical techniques that have broadened treatment options for this patient population, use of conven-tional radiotherapy and surgery will continue. In this systematic review, we attempted to establish whether the literature provides information regarding the timing of combined surgery and radiation in a patient with primary or metastatic neoplasia of the spine. Because of the paucity of literature in regards to our research questions, we also reviewed the general medical and basic science literature for additional supporting evidence.

Timing of surgery after radiotherapy. Among the many variables that influence wound healing, two issues appear to have special importance in patients with primary or secondary spine neoplasia who have received preoperative radiotherapy: the total radiation dose and the radiation-surgery time interval (39). In patients with malignant neoplasia of the spinal column, the spinal cord tolerance to radiation determines the maximal radiation dose.

The radiation-surgery time interval was the subject of early studies by Zelman *et al* (39), who demonstrated in a rat model

Table III. Timing of radiotherapy after surgery.

Refs.	Description	Level of evidence (in relation to the primary question)	No. of patients meeting inclusion criteria	Treatment	Results	Conclusion
Bach *et al* (31)	Retrospective	Level III	91	-Laminectomy followed by radiotherapy -Surgery-radiotherapy time interval was 5-8 days	-No patients were reported to suffer wound-related complications	
Gilbert *et al* (32)	Retrospective	Level III	65	-Laminectomy followed by radiotherapy -7 patients had additional preoperative radiotherapy	-7 patients suffered wound-related complications -Surgery-radiotherapy time interval was 5 days	Problem: not specified whether the patients that had complications were from the preoperative radiotherapy group.
Hall *et al* (33)	Retrospective	Level III	160	-154 patients had a laminectomy followed, when appropriate, by radiotherapy, usually 1 week after the surgery	-No patients were reported to suffer wound-related complications	
Landman *et al* (34)	Retrospective	Level III	127	-Laminectomy followed by radiotherapy -Surgery-radiotherapy time interval was 2-3 weeks	-No patients were reported to suffer wound-related complications	
Laohacharo-ensombat *et al* (35)	Retrospective	Level III	30	-29 patients had a transpedicular vertebrectomy and circumferential fusion -1 patient was operated through a combined anterior-posterior approach -All patients had postoperative radiotherapy -Surgery-radiotherapy time interval was 2 weeks	-2 wound infections, 1 deep and 1 superficial; it was not specified whether these occurred in a posterior or anterior wound -No patients suffered wound dehiscence	

Table III. Continued.

Refs.	Description	Level of evidence (in relation to the primary question)	No. of patients meeting inclusion criteria	Treatment	Results	Conclusion
Levy *et al* (36)	Retrospective	Level III	38	-Laminectomy followed by radiotherapy -Surgery-radiotherapy time interval was 1 week	-No patients were reported to suffer wound-related complications	
Onimus *et al* (37)	Not specified	Level III	57	-Patients underwent 60 procedures, 36 through an anterior approach and 24 through a posterior approach -Posterior procedures were mainly laminectomy with instrumented or non-instrumented fusion -42 patients had postoperative radiotherapy -Surgery-radiotherapy time interval was 8-10 days -Radiation was adminsitered at a dose of 18-20 Gy in 5 fractions over 5 days	-1 patient suffered wound infection, and 2 post-radiation skin necrosis	
Wise *et al* (20)	Retrospective	Level III	80	-Patients underwent 88 procedures -48 were through a posterior approach -41 patients had preoperative radiotherapy	-8 patients, who had all had preoperative radiotherapy, suffered wound infection, 7 of them in a posterior approach wound	Postoperative radiotherapy was not significantly associated with postoperative complications. Problem: surgical approach and number of patients that had surgery followed by radiotherapy were not specified, nor was the surgery-radiotherapy time interval.

Table III. Continued.

Refs.	Description	Level of evidence (in relation to the primary question)	No. of patients meeting inclusion criteria	Treatment	Results	Conclusion
Young *et al* (38)	Randomized prospective	Level III	16	-Laminectomy followed by radiotherapy vs. radiotherapy -Surgery-radiotherapy time interval was 1 week	-No patients suffered wound-related complications	
Ghogawala *et al* (7)	Retrospective	Level III	34	One-stage posterolateral decompression-stabilization procedure followed by radiotherapy	-4 patients suffered wound-related complications	Problem: surgery-radiotherapy time interval was not specified.
Shaw *et al* (28)	Not specified	Level III	2	One-stage posterolateral decompression-stabilization procedure followed by radiotherapy	-No patients suffered wound-related complications	Problem: surgery-radiotherapy time interval was not specified.
Sundaresan *et al* (29)	Not specified	Level III	5	Laminectomy followed by radiotherapy	-No patients suffered wound-related complications	Problem: surgery-radiotherapy time interval was not specified.

that wound tensile strength decreases when the surgery is done immediately or within one week after irradiation, compared with surgery that is done later. These findings were strengthened by Devereux *et al* (40) who showed similar results. These authors irradiated rats one week before or on the day of surgery and found the wound-breaking strength decreased by 59% compared with that of a control group of rats that were not irradiated.

We found only three clinical studies that discussed complications in comparison with the length of time between radiation and surgery. Wang *et al* (15) retrospectively reviewed a prospectively maintained database comprised of 140 patients who were treated with posterolateral transpedicular decompression for metastatic spine disease. Eighty-four patients had preoperative radiotherapy, of whom only 14 had radiotherapy within the month before surgery. The authors reported a total wound-related complication rate of 11.4% (16 patients), and found no statistically significant association between preoperative radiation therapy and postoperative infection (P=0.21). They found no increase in infection rate among patients who had radiation therapy within six weeks prior to surgery (P=0.29). The authors explained this lack of statistical significance as being due to the fact that only six of their patients underwent surgery within a week after radiotherapy.

Our group has reported outcomes in 42 patients who had posterolateral vertebrectomy for spine metastases (14) including 14 patients (33%) who had had preoperative radiotherapy more than one week prior to surgery. Three of the 14 (21%) had postoperative wound complications, as did seven other patients presented in the studies we reviewed. On the other hand, Ghogawala *et al* (7) showed a significant association between preoperative radiotherapy and postoperative complication rates in patients with metastatic spinal cord compression. They also reported a 46% complication rate in 13 patients whose surgery was performed within seven days of radiotherapy vs. a 20% rate in the 15 patients who had surgery more than a week after irradiation. Although there is a paucity of clinical data, we recommend waiting at least one week after radiation before surgery is undertaken in patients with spinal metastases. The evidence for the recommendation rests on data from a single study (7) and on general principles of the effects of radiation on wound healing from the basic science literature.

Timing of radiotherapy after surgery. Normal wound healing after surgery consists of three stages and requires two years. The mature scar will gain tensile strength equal to 80% of normal skin. The first week includes the inflammatory stage (0-4 days after injury) and the early phase of the proliferative stage (2-21 days after injury). Stages one and two are critical for wound healing, and very sensitive to radiation (41). These two early stages are characterized by active migration and proliferation of inflammatory cells, and then proliferation of collagen-producing fibroblasts, which have high sensitivity to radiation (42). If radiotherapy is given immediately after surgery, the inflammatory response is inhibited and the number of inflammatory cells is reduced (43). When there is exposure to radiation during the early proliferative phase, when fibroblasts normally proliferate and collagen production approaches its peak, deposition of collagen I and III is inhibited (43,44). The last stage of healing, granulation, begins five days after surgery. Granulation involves remodeling and maturation of the wound, processes that are less sensitive to radiation (45).

One week after the surgery, the cascade of wound healing has been initiated and collagen production by the fibroblasts has nearly peaked. Devereux *et al* (40) showed that wound breakdown strength in rats irradiated a week after wounding was similar to that in control rats that had no irradiation. Other research has suggested that the 'safe' surgery-radiation time interval in animals is even shorter, 24-48 h (46). In a parallel study of patients with soft tissue sarcoma, Ormsby *et al* (47) found that delaying brachytherapy by five to eight days after surgery decreased the wound complication rate from 48 to 14%. Although the directness of this evidence might be questioned because the radiation was not a randomized controlled trial, we felt the evidence was applicable to the primary question of our study and therefore was included.

In an assessment of possible factors associated with higher complication rates in patients undergoing surgery for metastatic spine disease, Wise *et al* (20) found that postoperative radiotherapy was not a statistically significant risk factor. Among the 51 case series involving patients with spine metastases who were treated with surgery followed by radiotherapy that were systematically reviewed for this study, only eight studies reported wound-related complications, with an average rate of 3.9% (range 0-16%) (7,21,24,28-30, 35,37). Only two reports detail both the complication rate and the surgery-radiotherapy time interval. Laohacharoensombat *et al* (35) described 30 patients who had radiotherapy 14 days after the surgery; only one patient (7.1%) developed a superficial wound infection. Young *et al* (37) reported on 16 patients who were given radiotherapy a week postoperatively; none developed wound-related complications.

Although skin that is wounded in surgery becomes a site of proliferation and repair, and remains a weak link until the wound finally reaches maturity approximately two years after the injury, it is the during the early stages of healing, which last about one week, that the risk of wound-related complications seems to be greatest. Irradiating a wound, especially in the first week after surgery, significantly interferes with the normal healing process.

Wound-healing problems are further amplified in oncology patients, who are often malnourished, may suffer from comorbid conditions, and may receive treatment involving corticosteroids, chemotherapy, or antiangiogenesis therapy. In such an unforgiving environment, the clinician has to weigh carefully the desire to control the tumor against the aim of preserving neurological function and maintaining a low complication rate.

Although there is a paucity of clinical data, the best available evidence would suggest avoiding radiotherapy for one week or longer after surgery for spinal metastases through a posterior approach may limit adverse effects on wound healing. The evidence for the recommendation rests on data from a single study involving brachytherapy (47), on the lack of identification of radiation administered at least a week after surgery as an independent risk factor for wound complications in the spine literature, and on general principles of wound healing biology. Although radiation after surgery is not commonly urgent, some tumors such as melanoma will

benefit from early therapy. Furthermore, logistic and patient scheduling issues also speak to the benefit of having guidelines for the timing of postoperative radiation.

Our study is limited by the small number of studies that discuss the optimal timing of surgical and radiotherapy procedures in relation to wound healing for patients with primary and secondary spine tumors. In addition, a critical appraisal of these studies would provide, at best, Class III evidence, according to the criteria for the classification of evidence developed by the U.S. Preventative Services Task Force (48). However, we believe that it is possible to make preliminary recommendations regarding our two questions. These recommendations provide the best available evidence to date, and may be applied in the context of clinical experience and circumstances, and patient preference pending stronger evidence.

This review provides a foundation on which to move forward with a large prospective multi-center database to generate the numbers and cohorts needed to address these two questions with a higher level of scientific integrity. A further limitation of our review is that the total dose of radiation was not available for analysis in the majority of the reviewed studies. Current radiation treatment planning often includes three-dimensional conformal radiation dosing or stereotactic spinal radiotherapy. These treatment modalities may minimize the radiation dose to the skin at the surgical incision site. These important issues will also require investigation in future studies.

In conclusion, the authors recommend that the radiotherapy-surgery time interval should be at least one week for patients with previous radiotherapy. In the opposite scenario, when radiotherapy is given after surgery, a time interval of at least one week should also be maintained.

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