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RESEARCH PAPER

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Local control of 1–5 fraction radiotherapy regimens for spinal metastases: an analysis of the impacts of biologically effective dose and primary histology

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ABSTRACT

Background: This analysis evaluates the impacts of biologically effective dose (BED) and histology on local control (LC) of spinal metastases treated with highly conformal radiotherapy to moderately-escalated doses.

Materials and methods: Patients were treated at two institutions from 2010–2020. Treatments with less than 5 Gy per fraction or 8 Gy in 1 fraction were excluded. The dataset was divided into three RPA classes predictive of survival (1). The primary endpoint was LC.

Results: 223 patients with 248 treatments met inclusion criteria. Patients had a median Karnofsky Performance Status (KPS) of 80, and common histologies included breast (29.4%), non-small cell lung cancer (15.7%), and prostate (13.3%). A median 24 Gy was delivered in 3 fractions (BED: 38.4 Gy) to a median planning target volume (PTV) of 37.3 cc. 2-year LC was 75.7%, and 2-year OS was 42.1%. Increased BED was predictive of improved LC for primary prostate cancer (HR = 0.85, 95% CI: 0.74–0.99). Patients with favorable survival (RPA class 1) had improved LC with BED ≥ 40 Gy ($p = 0.05$), unlike the intermediate and poor survival groups. No grade 3–5 toxicities were reported.

Conclusions: Moderately-escalated treatments were efficacious and well-tolerated. BED ≥ 40 Gy may improve LC, particularly for prostate cancer and patients with favorable survival.

Key words: stereotactic body radiation therapy (SBRT); palliative care; metastasis; spine; dose-escalation

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Introduction

Malignancies involving the spine are historically difficult to treat with single modality therapy. Chemotherapy and other systemic agents are often unable to promptly relieve pain [1]. Radiotherapy must respect the dose tolerance of the spinal cord to prevent the development of radiation myelopathy

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[2–5]. Finally, surgery can provide rapid relief but has a long recovery time which can delay the initiation of systemic therapy.

In the past decade, advancements in imaging and dose delivery have refined techniques to deliver escalated doses of radiation without violating organ at risk tolerance. One such technique is stereotactic body radiation therapy (SBRT), which is highly-conformal, high-dose radiation (≥ 5 Gy/fraction) delivered in up to five fractions [6, 7]. Importantly, the oligometastatic disease setting is a critical opportunity for SBRT, potentially providing the best chance to improve overall survival or even cure metastatic disease [8, 9]. Improved survival was demonstrated in the SABR-COMET trial; however, the trial reported grade ≥ 2 toxicity in the 29% of patients in the SABR arm, as well as 3 (4.5%) treatment-related deaths [10].

Beyond survival, SBRT has been shown to have a high rate of local control and has demonstrated effective palliation of pain [6, 11, 12]. Similarly, it has allowed for the possibility of re-irradiation [13–15]. Also encouraging are results for helical tomotherapy (HT), which delivers helical radiotherapy with sharp dose falloff like that seen with SBRT [16, 17].

Given the complexity and risk associated with these techniques, optimal patient selection is required. For patients with widely metastatic disease or poor prognosis, a range of other safe palliative regimens can be employed (e.g. 8 Gy in 1 fraction, 20 Gy in 5, 30 in 10, etc.). Even for patients selected for SBRT, a wide range of dose-fractionation schemes are utilized for spinal metastases, generally ranging from 1 to 5 fractions delivering 5–24 Gy per fraction [11, 18].

Common indications for spine SBRT include reirradiation and radioresistant histologies for the primary tumor. It is also possible that SBRT offers improved pain response compared to other treatment regimens. To address this questions, the SC.24 clinical trial directly compared complete pain response at 3 months post radiotherapy in patients receiving 20 Gy in 5 fractions to 24 Gy in 2 fractions. This has completed accrual, and preliminary results presented at ASTRO 2020 demonstrated improved rates of complete pain response at 3 and 6 months post-radiation . SBRT has also shown a faster reduction in pain values and lower visual analog scale (VAS) scores at 6 months, compared to 3D conformal radiotherapy [18].

We seek to contribute to the literature with this relatively large dataset from two institutions delivering a range of moderately escalated doses per fraction (≥ 5 Gy per fraction) using SBRT or HT. We aim to evaluate the impacts of biologically effective dose (BED) and primary histology on local control (LC) and determine a patient subset most likely to benefit from dose escalation.

Material and methods

Selection criteria and patient cohort

Patients were treated at two institutions with either linear accelerator-based SBRT or HT for spinal metastases from 2010–2020. At least one clinical or imaging follow-up was required for inclusion in the dataset. Patients treated with less than 5 Gy per fraction or 8 Gy in 1 fraction were excluded. Patients treated with more than five fractions were also excluded. In this way, we sought to exclude many of the conventional palliative doses used in these patients to focus on those receiving at least moderate dose escalation. Patients with primary spinal cord tumors or benign lesions were also excluded from further analysis. The institutional review board provided an exemption due to the research team following a previously approved protocol for retrospective studies. This exemption was subsequently approved by the institutional review board at the second institution.

Treatment delivery

Linear accelerator-based SBRT was delivered using a 6 MV photon beam, with dose prescribed to the planning target volume (PTV). PTV was defined as the gross tumor volume (GTV) plus a 3–5 mm margin, excluding the spinal canal. A full-body vacuum bag system was used for stabilization and consistency of treatment delivery. Daily on-board cone-beam CT was used generally 2–4 times during treatment for further assessment of patient positioning. Dose prescribed to the spinal canal was minimized, with a maximum of 2 Gy per fraction less than the prescribed dose allowed per fraction. Patients treated on the HT unit had treatment plans generated with an iterative planning technique on the HT treatment planning system (TomoTherapy Inc., Madison, WI, USA), using 6 MV photon

beams. Daily megavoltage CT imaging confirmed patient setup. For patients with entire vertebral body coverage in the target volumes, including a simultaneous integrated boost to gross disease plus margin, the higher dose PTV dose and volume is reported.

Outcomes and statistics

The primary endpoint of the study was local control. This endpoint was assessed as a binary value (local failure or disease control), allowing for utilization of the two-tailed t-test. Local control was assessed via spinal MRI or CT if MRI was contra-indicated. RANO criteria were used [20]. Local control was analyzed using the Kaplan-Meier method, assessing the time to local failure and censoring for the event of local failure. Secondary endpoints of toxicity and overall survival were also considered. Toxicity was reported according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Overall survival was most commonly assessed using the Kaplan-Meier method, with plots censored for patient death. The univariable log-rank test was used for assessment of statistical significance using this method. A threshold p value of 0.05 was used for the statistical methods. BED was calculated using the formula:

$$BED = total\ dose * (1 + dose\ per\ fraction / /alpha/beta\ ratio),$$

and an alpha/beta ratio of 10 Gy was used for all BED calculations.

Results

Patient characteristics

223 unique patients with 248 total treatment lesions were included in the dataset (Tab. 1). This consisted of 110 female (49.3%) and 113 male (50.7%) patients, with a median Karnofsky Performance Status (KPS) of 80 (50–100). Treatments involved a range of primary disease sites, with the three most common sites including breast (29.4%), non-small-cell lung carcinoma (NSCLC) (15.7%), and prostate (13.3%). Patients presented at a median age of 67.4 years at a median 42.8 months after primary diagnosis. Prior treatments were common in this cohort. Most patients had prior chemotherapy (80.6% of treatments), and a significant minority (32.7%) had prior radiotherapy at the location of spine treatment. Radiotherapy was delivered most commonly to the thoracic (39.5%) and lumbar spines (27.0%), but a significant fraction of cases involved the cervical (19.0%) or sacral spines (14.5%). 25 total cases involved spinal cord junctions. Of these, the lumbosacral junctional was most commonly treated (13 cases, 5.2%).

Table 1. The patient set is described

Characteristic	Incidence
Patients	223
Treatments	248
Gender	
Female	110/223 (49.3%)
Male	113/223 (50.7%)
Median KPS	80 (50-100)
Primary disease site	
Breast	73/248 (29.4%)
NSCLC	39/248 (15.7%)
Prostate	33/248 (13.3%)
Melanoma	15/248 (6.0%)
Renal	12/248 (4.8%)
Head and neck	10/248 (4.0%)
Other*	66/248 (26.6%)
Median time from primary diagnosis [months]	42.8 (0.43–501.91)
Median age at start of SBRT [years]	67.4 (31.4–88.7)
Prior chemotherapy	200/248 (80.6%)
Prior radiotherapy at that location	81/248 (32.7%)
Spinal region	
Cervical	47 (19.0%)
Thoracic	98 (39.5%)
Lumbar	67 (27.0%)
Sacral	36 (14.5%)
Junctions	
Cervicothoracic	7 (2.8%)
Thoracolumbar	5 (2.0%)
Lumbosacral	13 (5.2%)

*The most common other histologies included thyroid and sarcoma; KPS — Karnofsky Performance Status; NSCLC — non-small-cell lung carcinoma; SBRT — stereotactic body radiation therapy

Outcomes

Treatments included both linear accelerator-based SBRT (82.2%) and HT (17.7%). A median dose of 24 Gy (6–36 Gy) was delivered in a median 3 fractions (1–5). This correlated with a median BED of 38.4 Gy (9.6–79.2 Gy). The PTV was a median 37.3 cc (1.1–2436.0 cc).

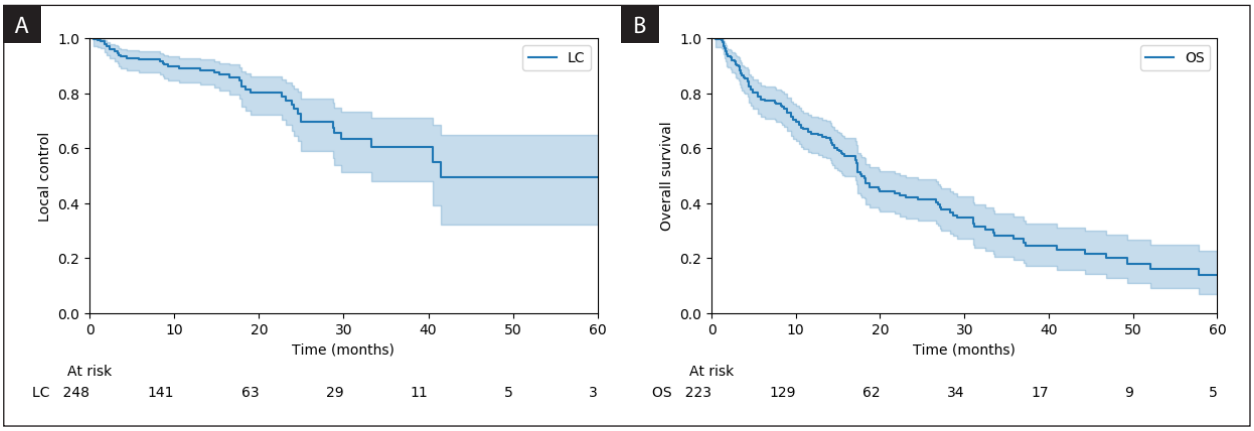

Figure 1. Local control (**A**) and overall survival (**B**) for the entire cohort are shown

Table 2. Treatment details and outcomes are tabulated

Treatment aspect or outcome	
Technique	
SBRT	204/248 (82.2%)
HT	44/248 (17.7%)
Median dose [Gy]	24 (6–36)
Median fractions	3 (1–5)
Median dose per fraction [Gy/fx]	7 (5–20)
Median PTV [cc]	37.3 (1.1–2436.0)
Median imaging follow-up [months]	9.74 (0.0–125.2)
Treatments with imaging follow-up	226/248 (91.1%)
Median clinical follow-up [months]	12.85 (0.0–128.2)
Treatments with clinical follow up	247/248 (99.6%)
2-year local control	76%
Local failures	44/248 (17.7%)
Crude local control	204/248 (82.2%)
Median time to local failure [months]	11.8 (0.5–41.5)
2-year overall survival	42%
Median overall survival [months]	13.7 (0.3–124.0)

SBRT — stereotactic body radiation therapy; HT — helical tomotherapy; PTV — planning target volume

Imaging follow-up was obtained after 91.1% of treatments, with a median duration of 9.7 months of imaging follow-up (0.0–125.2). Clinical follow-up was documented after 99.6% of treatments, with a median duration of 12.9 months (0.0–128.2). There were 44 total local failures (17.7%), correlating to a crude local control of 82.2%. Local failure occurred at a median 11.8 months (0.5–41.5 months) after the completion of radiotherapy. The 2-year local control via the Kaplan-Meier method was 75.7% (Fig. 1). The 2-year overall survival via the Kaplan-Meier method was 42.1% (Tab. 2).

Toxicity

64 patients (28.7%) experienced a treatment side effect. Of these, only 6 total instances of toxicity > grade 1 were reported. These side effects were all grade 2, and they all occurred in the SBRT group. HT had a statistically significant decrease in highest grade toxicity ($p = 9.18*10^{-5}$), largely driven by the six cases of grade 2 toxicity in the SBRT group. These side effects consisted of acute pain (n = 1), acute dysphagia (n = 2), and chronic pain (n = 3). There were no cases of radiation myelopathy.

Risk stratifications

First, the two techniques included in the cohort were compared. No difference was noted on Kaplan-Meier analysis (p = 0.47) considering the local control achieved with SBRT compared to that with HT. Junctional tumors were also compared to the non-junctional tumors, and no statistically significant difference in local control was found. PTV > 30 cc was indicative of increased local failure on two-tailed t-test (p = 0.01), but this trend was not persistent on Kaplan-Meier analysis (p = 0.80). The dose per fraction was also assessed via Kaplan-Meier analysis, and no difference in local control were determined on comparison of 5–5.5, 6–6.5, 7, 8, and greater than 8 Gy per fraction.

When local control was stratified by primary histology, however, significant differences were noted (Fig. 2). These differences were further stratified by increased BED, and treatments involving primary prostate cancer demonstrated improved local control with increased BED (HR = 0.85, 95% CI: 0.74–0.99). Other tumor histologies, including breast cancer (HR = 1.06, 95% CI: 0.93–1.20) and

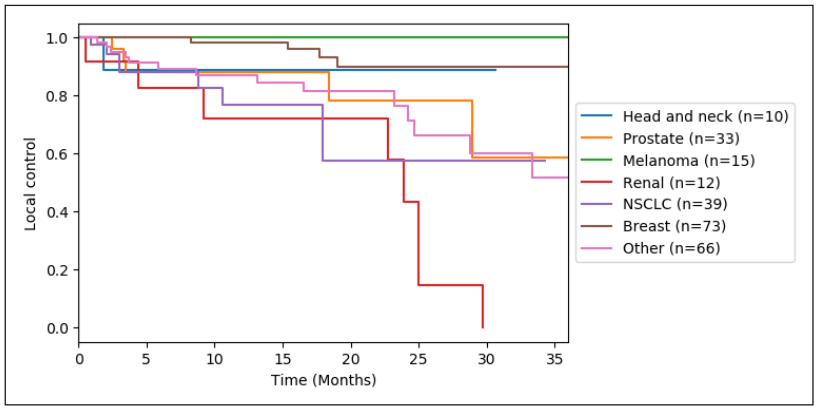

Figure 2. Local control was stratified by primary histology

Table 3. Important outcomes of the biologically effective dose (BED) of 40 Gy stratification are demonstrated

	BED < 40 Gy 2-year LC	BED ≥ 40 Gy 2-year LC	Log-rank p-value
Histology			
Breast	89.8%	86.5%	0.32
NSCLC	45.0%	65.5%	0.37
Prostate	51.6%	100.0%	0.02
RPA Class			
1	66.4%	82.2%	0.05
2	85.7%	73.1%	0.90
3	93.8%	51.6%	0.08

LC — local control; NSCLC — non-small-cell lung carcinoma; RPA — recursive partitioning analysis

NSCLC (HR = 1.06, 95% CI: 0.95–1.18), failed to demonstrate a difference in local control using this BED threshold or considering BED as a continuous variable on Cox regression. Patients with primary NSCLC demonstrated a non-statistically significant increase in 2-year LC with dose escalation (65.5% *vs.* 45.0%), however, and patients with primary breast cancer demonstrated 2-year LC > 85%, regardless of the doses used (Tab. 3). Single-fraction treatments also did not show a difference in local failure rate relative to multi-fraction regimen (p = 0.30), but there were only 17 single-fraction treatments in this dataset. Five-fraction regimens also did not have increased local failure, relative to shorter treatment regimens (p = 0.35).

RPA classes

The dataset was finally divided according to the RPA classes previously analyzed by Chao et al. to stratify by overall survival (1). Class 1 consisted of patients with > 30 months from primary disease diagnosis and KPS > 70; class 2 included patients with > 30 months from primary diagnosis and KPS ≤ 70 or ≤ 30 months from diagnosis and age < 70 years; class 3 involved ≤ 30 months from diagnosis and age ≥ 70 (Supplementary File — Fig.1). Patients in class 1, 2, and 3 demonstrated 2-year OS of 44.2%, 41.6%, and 38.7%, respectively. These classes failed to demonstrate significant differences in local control; however, treatments that involved the delivery of a BED of at least 40 Gy had statistically significant improvements in local control for patients in the favorable survival group (Class 1, p = 0.05, Fig. 2). Patients in the intermediate or poor survival groups did not demonstrate this local control benefit with increased BED (p = 0.90 and 0.08, respectively). Stratification by BED ≥ 40 Gy was not predictive of improved survival in any of the RPA classes (p = 0.51, p = 0.53, and p = 0.81, respectively).

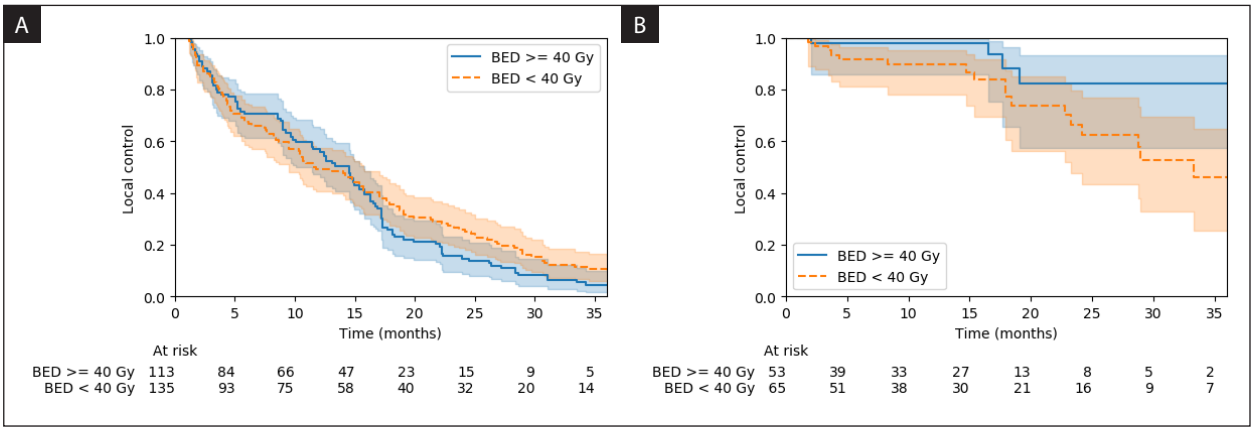

Figure 3. Key stratifications of the RPA classes by biologically effective dose (BED) ≥ 40 are shown. **A.** This threshold failed to demonstrate statistical significance when applied to the entire cohort (p = 0.19); **B.** However, BED ≥ 40 Gy showed statistically significant improvement in local control in class 1 (p = 0.05)

Discussion

In this multi-institutional study of patients treated with moderately dose escalated radiation to spinal metastases, we observed encouraging outcomes, with 2-year LC 75.7% and minimal toxicity for a wide range of doses [21, 22]. In patients with favorable survival (RPA class 1) and those with prostate cancer, a benefit of increased BED_{10Gy} beyond approximately 40 Gy was observed.

These results can assist in stratifying patients for treatment escalation from other standard palliative treatment regimens [23, 24]. The key separation of the LC Kaplan-Meier curve for class 1 patients stratified by BED occurred around 18–24 months, suggesting that increased doses of SBRT and HT may lead to a more durable local control response [1]. Various studies suggest a range of improved outcomes using spine SBRT compared to 3D conformal techniques, including faster and potentially improved pain response, as well as higher rates of complete pain response at 3 and 6 months post-radiation [18, 19]. Additionally, our findings support an increased role of highly conformal techniques for patients with favorable survival. The fact that the dose per fraction demonstrated no relationship with local control may also suggest the BED is a more holisitic way to consider dose delivery in this setting.

This result also supports the hypothesis that the primary disease histology of spinal metastases should impact therapeutic decision-making [25–29]. Patients with certain tumor histologies, including prostate cancer in our series, may have increased benefit from dose escalation. In the primary treatment setting of patients with less favorable histologies and poor overall predicted survival, a shared decision-making model should be employed to consider the role of other radiotherapy techniques (as this patient group may not receive maximal benefit from dose escalation). However, in the age of an ever increasing number of targeted agents and immunotherapies resulting in prolonged survival, more and more histologies will benefit from the more durable local control following SBRT.

Notable differences were appreciated in the dataset between different histologies and the outcomes of dose escalation (BED ≥ 40 Gy), consistent with prior literature [29, 30]. Patients with primary breast cancer had high rates of local control, regardless of the dose delivered (2-year LC of 89.8% and 86.5% with lower and higher BED, respectively). Prostate cancer patients, on the other hand, demonstrated improved local control with dose escalation (p = 0.02). These patients may derive particular benefit from ablative doses of radiotherapy, as demonstrated by the ORIOLE trial [31]. There likely was an insufficient number of patients with NSCLC to detect a difference, but patients with dose escalation demonstrated a non-statistically significant increase in 2-year LC (65.5% *vs.* 45.0%). It is possible that the inclusion of more patients with primary NSCLC would have allowed us to demonstrate a conclusive improvement with dose escalation for these patients, as well. Overall, these results

are hypothesis-generating, but they argue against the pursuit of a single optimal dose-fractionation scheme for all patients presenting with spinal metastases. Further personalization of patient care is required, and a more nuanced understanding of the interplay between primary histology particularly considering types, subtypes, and molecular mutations and patient prognosis is needed. We strongly encourage dose escalation trials to further our understanding as a field.

Both SBRT and HT led to encouraging results in this setting. This result suggests that HT and other techniques that result in highly conformal treatment delivery can also be considered in this setting, in addition to SBRT. There was also no major difference in toxicity between these techniques. The use of moderately escalated doses should be further studied, secondary to the encouraging toxicity results in comparison with the higher doses utilized in the SABR-COMET trial [10].

Lastly, the volume of radiation treatment required appeared to impact LC. A PTV > 30 cc led to increased local failure on univariate analysis but not on Kaplan-Meier analysis. This result is inconclusive but may suggest that larger treatment volumes may have lower local control, and consideration should be given to treatment intensification or alternative multimodality approaches in such cases. It is also possible that increased volume [32] may be the driving factor regarding some reports of worse outcomes with junctional tumors or multi-level treatments [33].

The key limitations of this analysis include the varied dataset and the retrospective nature of the data collection. There were varied doses and treatment techniques involved in this analysis, and it is possible that there are some important differences between them not identified by this study. These patients also had relatively shorter follow-up that may have reduced our ability to detect the further impact of more durable local control. Even so, the identification of improved local control in patients with favorable survival outcomes is encouraging. Finally, there were many tumors whose histologies were not captured by our analysis. This reflects the heterogeneous nature of radiotherapy treatments for spinal metastases. We strongly encourage further collaborative efforts to develop large databases of patients treated with similar techniques to better assess the dose response of particularly common tumor histologies (e.g. prostate, NSCLC, and breast).

Conclusions

Treatment of spinal metastases with a range of moderately escalated doses per fraction using modern radiation techniques was efficacious and well-tolerated. BED ≥ 40 Gy may improve LC, particularly for prostate cancer and patients with favorable survival; however, a multi-disciplinary approach may be necessary for larger tumor volumes. The optimal dose-fractionation scheme for spine SBRT and HT is yet undetermined, and it is likely that the ideal treatment regimen depends on the primary tumor histology and overall patient prognosis.

Conflicts of interest

The wife of R.O.K. is a senior technical product manager at GE Healthcare.

Funding

Not applicable.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

None declared.

Ethics approval

The institutional review board provided an exemption due to the research team following a previously approved protocol for retrospective studies. This exemption was subsequently approved by the institutional review board at the second institution.

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