

Scientific Article

Radiation Therapy in Conjunction With Surgical Stabilization of Impending or Pathologic Fractures Secondary to Metastasis: Is There a Difference Between Single and Multifraction Regimens?



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Abstract

Purpose: Patients who undergo surgical stabilization for impending or pathologic fractures secondary to metastasis are often treated with radiation therapy to the involved site. We sought to retrospectively analyze outcomes from single versus multifraction regimens of radiation therapy in this setting.

Methods and Materials: From our institutional radiation database, we identified 87 patients between 2004 and 2016 who had an impending or pathologic fracture from metastatic disease and who underwent surgical fixation in conjunction with either neoadjuvant (within 5 weeks before surgery) or adjuvant (within 10 weeks after surgery) radiation therapy, representing 99 total treatment sites. Patients were included on the basis of intention to treat with bimodality therapy. Baseline patient characteristics were compared using 2-sided *t* tests and Fisher's exact tests. Cumulative incidence of local failure, reirradiation, and reoperation were calculated using the Fine-Gray method for competing risks. Freedom from complication was calculated using the Kaplan-Meier method.

Results: Baseline characteristics between the single (*n* = 52) and multifraction (*n* = 47) cohorts were similar with the exception of higher rates of synchronous bony metastasis (83% vs 60%, *P* = .01) and female patients (71% vs 43%, *P* = .004) in the single fraction cohort. There was no significant difference in overall survival between treatment groups. After a median follow-up of 13 months, there was no significant difference in the single and multifraction cohorts, respectively, in the 1-year cumulative incidence rates of local failure (4% vs 7%, *P* = .58), reirradiation (5% vs 4%, *P* = .95), reoperation (4% vs 0%, *P* = .30), or 1-year freedom from complication (90% vs 95%, *P* = .40).

Conclusions: This is the first study comparing outcomes between single and multifraction radiation therapy in conjunction with surgical stabilization of an impending or pathologic fracture. We found no difference in outcomes between single and multifraction regimens in this setting. Given these findings, single fraction perioperative radiation therapy may be a viable treatment option in appropriately selected patients pending prospective validation of these findings.

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Introduction

In 2020, there will be an estimated 1.8 million new cancer diagnoses in the United States,¹ of which an estimated 151,000 will be diagnosed with or develop metastatic bone disease,^{2,3} and up to 34% of these patients will be diagnosed with or develop a pathologic fracture.^{4,5} Impending and pathologic fractures can lead to significant pain, neurologic dysfunction, and a decline in performance status.⁶ Management has historically been surgical fixation, with the goal of local tumor control, restoring structural integrity, and improving function.⁷ Several studies have demonstrated that incorporating radiation therapy (RT) with surgical fixation of impending or pathologic fractures has been associated with improved overall survival, functional status of the affected extremity, decreased rates of reoperation, and lower rates of local failure.⁸⁻¹¹ Given these results, treating pathologic and impending fractures with surgical fixation and perioperative RT has become common clinical practice.

To date, there have been no published reports comparing single versus multifraction RT regimens for patients with impending or pathologic fractures treated with surgery in conjunction with RT. Given this lack of data, we sought to assess differences in the rates of local failure, reirradiation, reoperation, and complications in this clinical setting.

Methods and Materials

With institutional review board approval, we conducted a retrospective review of patients with impending or pathologic bone fractures secondary to biopsy-proven metastases who underwent surgical fixation and perioperative RT treated between 2004 and 2016. Patients were identified using billing codes, which were then matched to an institutional database of patients treated with radiation. Patients were considered to have an impending or pathologic fracture requiring surgical fixation based on imaging review by both a radiologist and orthopedic surgeon and clinical examination by an orthopedic surgeon. The determination of need for prophylactic surgical fixation was not made using strict quantifiable criteria, but typically was the product of a combination of factors such as lytic tumor, tumor location, extent of cortical destruction, and pain with movement or weight bearing.

Patients were included if radiation to the surgical site occurred within 5 weeks before or 10 weeks after surgery with neoadjuvant or adjuvant intent, respectively, and the patient completed the planned course of therapy. Patients were excluded if radiation was not delivered to the area of surgical fixation, postoperative radiation was performed due to a preceding surgery's failure, or if surgery was performed due to failure of the preceding RT course

(eg, incomplete pain relief or fracture after radiation). Cohort selection with inclusion and exclusion criteria is shown in [Figure 1](#).

Clinically relevant data were extracted from the electronic medical record, including patient demographics, tumor histology, extent of metastatic disease, type of surgery performed, performance status, vital status, and last follow-up date. Patients were considered to have a radioresistant histology if the primary histology was renal cell carcinoma, melanoma, sarcoma, colon adenocarcinoma, or papillary thyroid carcinoma. Clinical events, including local failure, complications, reoperation, and reirradiation, were also recorded.

Length of follow-up, time to local failure, time to a complication, and time to reoperation for each surgical site were defined as the time from initiation of surgery or radiation, whichever was performed first, until the respective event occurred or censored at death or last follow-up. Local failure was defined based on follow-up imaging showing tumor progression or recurrence at the surgical site or development of new or worsening symptoms at the surgical site that were deemed by the surgeon or radiation oncologist to be due to tumor progression, the latter requiring further intervention either surgically or with repeat RT. Complications were defined clinically or by imaging. Two-sided *t* tests and Fisher's exact tests were performed to compare baseline patient cohort characteristics. Freedom from complication was estimated using the Kaplan-Meier method, and median survival estimated by reverse Kaplan-Meier method with comparisons performed using Wilcoxon rank-sum testing. Cumulative incidences of local failure, reirradiation, and reoperation were calculated using the Fine-Gray method for competing risks with comparisons reported using Gray's test. Risk factors were assessed using the univariable Cox proportional hazard method. Statistical analysis was performed in STATA/IC-14.

Results

We identified 216 patients with a malignancy who had undergone 304 surgical fixations and had also been treated with RT. Of these surgical sites, reasons for exclusion included not receiving radiation to the surgical site (131), radiation delivered outside of the prespecified date range (37), insufficient documentation (23), or radiation or surgical fixation performed due to failure of preceding therapy (14). The remaining study population included 87 patients with 99 surgical procedures that met our inclusion criteria. Within this study population, 11 patients had multiple surgical sites. Patient cohort characteristics are illustrated in [Table 1](#).

Patients in the single and multifraction cohorts were similar regarding median age, performance status, the proportion of patients with pathologic fractures, patients

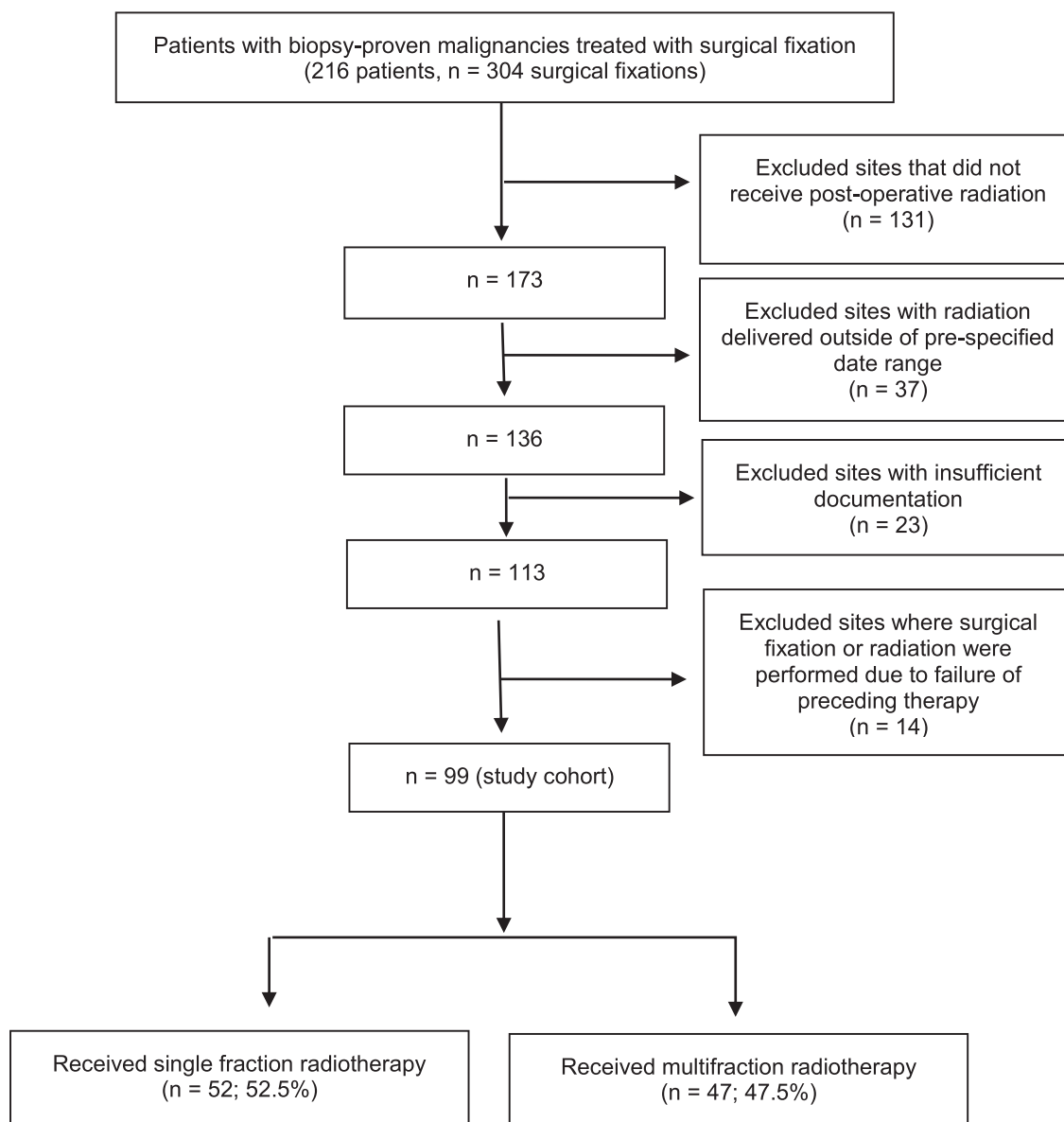


Figure 1 Inclusion and exclusion criteria.

who received preoperative versus postoperative RT, proportion of patients with multiple surgical sites, and the presence of synchronous visceral metastasis. There were more women (71% vs 43%, $P = .004$) and patients with synchronous bone metastasis (83% vs 60%, $P = .01$) in the single fraction cohort compared with the multifraction cohort. None of the mentioned clinical factors were found to be associated with time to local failure, time to reirradiation, time to reoperation, or time to complication, as shown in Table 2. The modal dose used in the single fraction group was 8 Gy in 1 fraction compared with 30 Gy in 10 fractions in the multifraction arm.

With a median follow-up of 13 months and median overall survival of 17 months, 3/46 (7%) patients in the single fraction cohort and 5/41 (12%) patients in the multifraction cohort were alive at the time of analysis.

Overall survival was not statistically significant between the single and multifraction cohorts ($P = .50$). There was no significant difference between the single and multifraction cohorts, respectively, in the 1-year cumulative incidence rates of local failure (4% vs 7%, $P = .58$), reirradiation (5% vs 4%, $P = .95$), reoperation (4% vs 0%, $P = .30$), or 1-year freedom from complication (90% vs 95%, $P = .40$), as shown in Figure 2. It should be noted that there were multiple events that occurred more than 4 years from the time of original treatment, but there was similarly no significant difference in the crude incidence of local failure (15% vs 19%, $P = .62$), reirradiation (12% vs 11%, $P = .89$), reoperation (10% vs 4%, $P = .30$), or freedom from complication (10% vs 9%, $P = .85$). There was also no significant difference between the single and multifraction cohorts, respectively, in the median time to

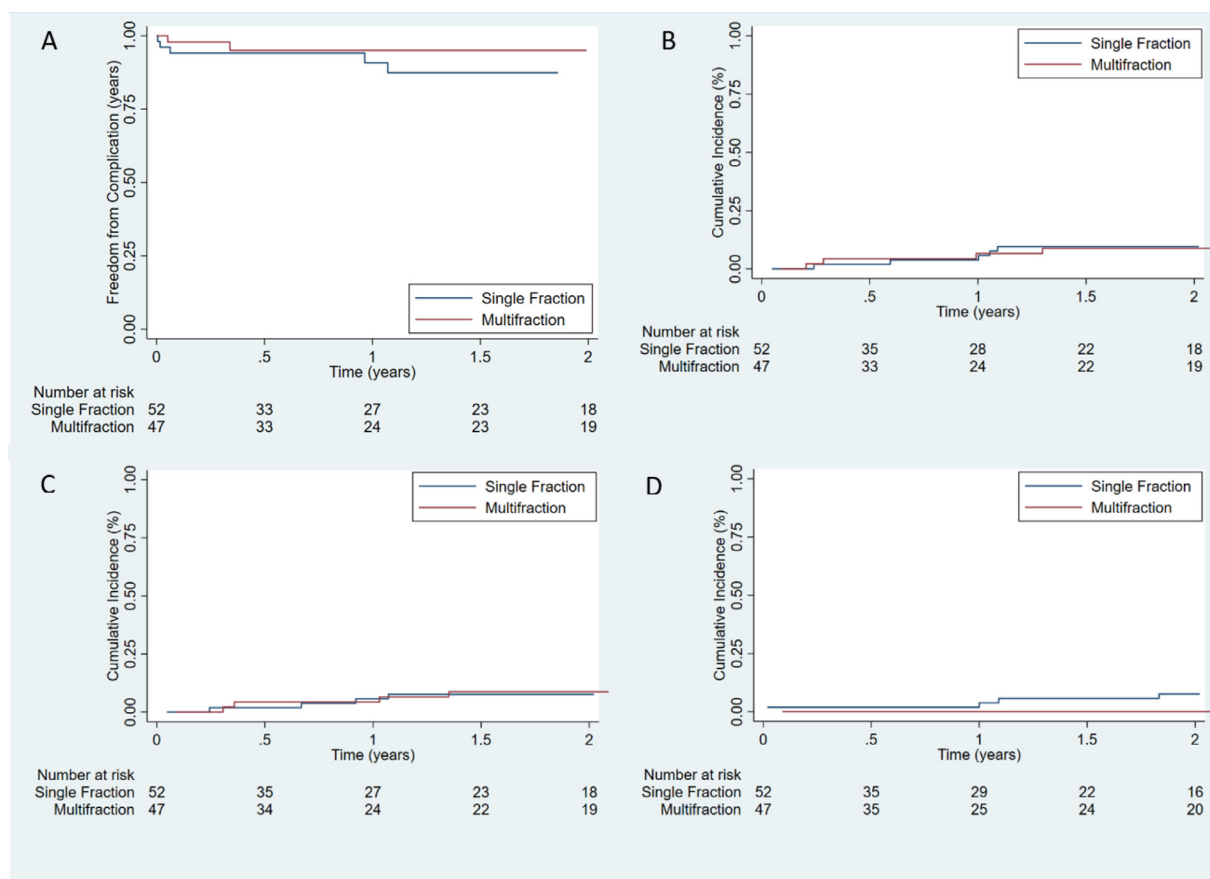


Figure 2 Kaplan-Meier curves of single fraction and multifraction patient cohorts showing (A) freedom from complication. Cumulative incidence curves of (B) rates of local failure, (C) rates of reirradiation, and (D) rates of reoperation.

local failure (12 vs 8 months, $P = .71$), reirradiation (12 vs 7 months, $P = .73$), reoperation (12 vs 8 months, $P = .41$), or complications (12 vs 7 months, $P = .49$).

Of the patients who had multiple surgical sites, 5 were treated with multifractionated RT to all sites, 5 patients were treated with a single fraction to all sites, and 1 patient received a multifractionated course to 1 site and a single fraction course to another. The primary site of disease in patients with multiple surgical sites included breast (4), kidney (3), lung (2), bladder (1), and sarcoma (1). Patients who had multiple surgical sites were not more likely to receive single fraction versus multifractionated RT (hazard ratio, 1.09; $P = .38$). None of the patients with multiple surgical sites experienced local failure, reirradiation, or reoperation. One patient who received all single fraction treatments experienced a postoperative infection before RT. The median length of follow-up within this group was 7 months.

Indications for reoperation in the single fraction cohort included 2 cases of arthritis and single cases of osteonecrosis, hardware failure, and local failure. Both multifraction cohort reoperations were due to local failure. All 7 patients who required reoperation had previously received postoperative RT, and 1 patient developed a surgical site infection. Complications in the single fraction

cohort included single intraoperative periprosthetic fracture cases, hardware failure, postoperative pain, and 2 cases of postoperative infection. All 4 complications in the multifraction cohort were related to hardware failure.

Discussion

The role of single fraction radiation has been well-established by multiple randomized controlled trials in patients with uncomplicated bone metastases. A recent meta-analysis of treatment outcomes with single versus multifraction RT without surgery for uncomplicated bone metastases found only a 3% absolute difference in response rates favoring multifractionated regimens and a 2.4 pooled odds ratio of reirradiation if treated with a single fraction course of RT, with otherwise equivalent outcomes.¹² Our study extends this concept further by providing evidence for the role of single fraction radiation in patients with complicated metastases requiring surgical intervention.

The median survival of patients in our study compares favorably to other study cohorts with surgical fixation and preoperative radiation,^{8,11,13,14} suggesting the

Table 1 Patient demographics by cohort

	Single fraction	Multifraction	P value
Number of sites treated	52	47	-
Median age (years)	58 (range, 27-87)	57 (range, 28-80)	.53
Sex, female	71%	43%	<.01
Median ECOG	2 (1-3)	2 (1-3)	.95
Pathologic fracture	25%	38%	.16
Preoperative radiation therapy	15%	28%	.14
Synchronous bone metastases	83%	60%	.01
Synchronous visceral metastases	64%	51%	.22
Modal radiation therapy dose (Gy)	8 (range, 8-12)	30 (range, 15-39)	-
Modal radiation therapy fractions	1	10 (range, 5-15)	-
Median follow-up (months)	13 (IQR 3-27)	16 (IQR 4-40)	.57
Histologies			-
Breast	23	11	
Lung	14	7	
Kidney	5	10	
Prostate	2	2	
Bladder	0	4	
Multiple myeloma	3	4	
Endometrial	0	1	
Melanoma	2	2	
Pancreas	2	0	
Sarcoma	0	4	
Thyroid	0	1	
Colon	1	1	
Metastatic site			-
Femur/hip	41	39	
Humerus	8	5	
Tibia	3	2	
Ulna	0	1	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range.

generalizability of our results. Although some studies have shown a trend toward improved overall survival with the addition of RT to surgical fixation,^{8,15} we would generally not expect a local palliative treatment in the setting of metastatic disease to improve overall survival. This might be theoretically possible if the addition of RT were to decrease the risk of pathologic fracture, risk of

reoperation, or improve functional/performance status. Unfortunately, there are minimal data on survival outcomes that delineate differences in outcomes between those patients treated with surgery alone and those who receive RT, making comparisons difficult. Because the question addressed by this study was regarding single versus multifraction treatment, we did not include a

Table 2 Univariable analysis of patient characteristics and treatment outcomes

	Time to local failure		Time to reirradiation		Time to reoperation		Time to complication	
	HR	P	HR	P	HR	P	HR	P
Multifraction radiation therapy	1.09	.86	0.84	.78	0.79	.23	0.79	.72
Age	1.00	.85	1.02	.35	1.04	.54	1.04	.13
ECOG	0.80	.55	1.4	.43	1.05	.16	1.05	.92
Synchronous visceral metastasis	2.3	.10	0.94	.92	1.2	.30	1.2	.80
Synchronous bone metastasis	2.0	.27	1.8	.45	1.4	.09	1.4	.68
Pathologic fracture	0.92	.88	1.9	.31	2.5	.78	2.5	.19
Preoperative radiation therapy	1.8	.36	0.61	.45	1.1	.87	1.1	.87
Radioresistant histology	1.8	.25	1.2	.81	2.7	.20	2.3	.23
Multiple surgical sites	0.56	.44	0.9	.31	0.7	.61	1.07	.19

Abbreviations: ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio.

surgery-only cohort in the analysis to assess the benefit of perioperative RT.

The 17% overall local failure rate observed in this cohort matches the 17% crude incidence reported in 2 other studies on postoperative RT after surgical fixation of bone metastasis with similarly long follow-up times.^{10,16} We did not identify any risk factors for local failure, in contrast to previous reports that identified age, sex, operation method, pathologic fracture, and preoperative RT as being associated with an increased risk of local failure.¹³

Our overall reirradiation rate is comparable to the 9.5% crude incidence rate of reirradiation reported by Drost et al,¹⁰ but there are no published reports comparing reirradiation rates based on RT fractionation in patients who had surgical fixation. We found no association between fractionation and rate of reirradiation. This is in contrast to the difference in reirradiation rates seen in single versus multifraction regimens for noncomplicated bone metastases as reported in the Rich et al¹² meta-analysis. This difference seen in the randomized trials may be attributed to an increased willingness of radiation oncologists to offer reirradiation to patients who were previously treated in a single fraction. Alternatively, durability of pain response may be less in single-fraction patients with uncomplicated bone metastases, whereas this differential in response duration may be tempered in patients who have undergone stabilization such as in our cohort.

In our study, 7% of patients required reoperation, within the 2.7% to 13% crude incidence range reported previously.^{8,10,13-15,17,18} Although our reoperation rate is higher than the 2.9% and 2.7% rates of reoperation reported by Townsend et al⁸ and Drost et al,¹⁰ respectively, it compares favorably to the 10% rate reported by Wedin et al¹⁵ after surgery alone. Minimizing reoperation rates is important to reduce surgical complication risk and end-of-life time spent in the hospital. Jacofsky et al¹⁸ found that revision surgeries are associated with a 14% incidence of serious complications, including deep infections, myocardial infarction, or cerebrovascular accident. They noted that 21% of patients who had previously been treated with RT developed deep prosthetic infections requiring a third operation, while patients without prior radiation had no deep prosthetic infections. In our study, 1 of 7 patients who required reoperation developed a surgical site infection.

The 9% rate of complications observed in our cohort is similar to the 9.9% to 23.8% crude incidence rate of complications reported in other studies of patients treated with surgical fixation with or without radiotherapy.^{13-15,17-19} Although multiple surgical studies have identified RT as a factor strongly associated with postoperative complications,^{13,18,20} our perioperative RT cohort had similar complication rates as reported in studies with surgery alone.⁹ Prior reports have shown an increased

risk of implant breakage with preoperative radiation, which we did not find in our cohort.¹³

This study has several limitations, including its retrospective nature and small population size. We could not account for the effect of single fraction versus multifractionated RT on subjective pain response or functional status due to variability in reporting. Given the near uniformity of systemic therapy among patients with metastatic disease and the heterogeneity of histologies included we did not account for the use, type, or timing of systemic therapy. This study included a subgroup of patients who had multiple surgical sites; however, these patients were evenly distributed among the single fraction and multifraction cohorts. These patients may have had a higher burden of disease, and we did find that patients in the single fraction cohort had a higher rate of synchronous bone metastasis. The limitations of follow-up length with terminal or hospice patients, along with the wide geographic distribution of patients treated at our institution, could mean that not all events are captured within our regional network, which could result in underestimation of event rates. This study is also limited in the fact that it does not account for underlying tumor size, lesion complexity, or extent. If there is a benefit to the fractionated courses for larger and more complicated lesions, this might not have been seen if these patients were preferentially treated with extended radiation courses due to pre-existing physician bias.

Conclusions

This is the first study comparing outcomes between single versus multifraction RT in conjunction with surgical stabilization of an impending or pathologic fracture. Our results suggest no difference between single and multifractionated RT courses regarding overall survival, local failure, reirradiation, reoperation, or complications. Single fraction perioperative RT reduces the time patients with limited life expectancy spend in the hospital system, reduces the patient's financial burden, and is a more efficient utilization of health care resources. Until a prospective randomized study can be performed, single fraction perioperative RT is a reasonable treatment approach for appropriately selected patients. However, a further prospective investigation is warranted to confirm these findings.

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