ORIGINAL ARTICLE

The benefit of surgical management of colorectal carcinoma bone metastases

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Abstract

Background/Objective: Metastatic colorectal carcinoma to bone rarely requires surgical intervention, and is infrequently studied. Aggressive surgical resection is sometimes empirically recommended in these patients, although there is no proven benefit for patient survival. Our hypothesis was that there is survival advantage conferred by resecting bone metastases (BM) when surgery is necessary.

Methods: We performed a retrospective review of a prospectively collected database and identified 39 patients with bone metastases in the appendicular skeleton requiring surgery. Patients underwent surgery because of intractable pain, impending pathologic fracture, and/or pathologic fracture at presentation.

Results: Median survival after complete resection of bone metastasis was higher (8 months) than for patients who had surgery, but did not have bony metastases completely excised (3 months, $p = 0.014$); and in surgical patients who had solitary bone metastasis at presentation ($p = 0.023$) compared with multiple bone involvement. There were no perioperative deaths. Additional skeletal surgeries were only required for patients (4 out of 39) with local recurrences. In cases of local recurrence, the median time to progression was 19 months.

Conclusions: Surgery for bone metastasis in colorectal carcinoma is well tolerated, and can be considered for palliative care. Compared with other surgical techniques, complete bone-metastasis resection is associated with longer overall survival, and with longer recurrence free survival.

Key words

Bone, Metastasis, Colorectal cancer, Skeletal, Surgery

1 Introduction

Colorectal cancer is the third most common cancer in the US and the third most common cause of death from cancer [1]. However, a bone metastasis (BM) requiring surgical intervention is extremely rare. Studies have shown that metastasis to the liver and lung develop earlier and more frequently than in bone, and are perhaps a prerequisite for BM formation [2, 3]. Prognosis is poor following BM formation, with most patients dying in less than a year [4-8].

We were unable to find publications that focus on the outcomes of surgery for bone metastases in colorectal carcinoma. In contrast, there have been studies to determine prognostic variables with metastasis to other organs [4-6, 9, 10]. The incidence of BM from colorectal cancer ranges from 9%-11% in autopsy cases, to 5%-11% in clinical series [4, 5, 8, 11-14]. Several studies correlate the site and number of metastasis to other organs with patient survival [5, 9, 13, 15-17]. Skeletal metastases most often occur in the spine [5, 16]. Proximal long bone involvement (femur and humorous) is seldom observed, and distal long bone involvement (tibia, fibula, radius, ulna, hands, feet) is exceedingly rare [1, 7, 14, 16, 18-21].

The treatments most often used for BM are non-surgical [5]. Radiotherapy is often cited as the most effective therapy for painful skeletal metastases [5, 7, 17, 22]. Surgery is viewed as being palliative [5, 7-9, 17, 22]; and the guidelines determining whether the surgical resection of BM should be complete or partial/incomplete are empirical. Though not well documented, the decision on whether to completely resect a bone metastasis is made by the surgeon, and presumably is largely based on the technical difficulty of the procedure.

The purpose of this study was to assess the indications and adequacy of operative interventions for skeletal metastases from colorectal carcinoma, and the prognosis for patients following surgery. We hypothesized that there is a survival advantage for completely resecting bone metastases. For the following study, a series of patients at a single institution was analyzed to determine the dependence of overall patient survival, disease progression, and complications from surgical intervention, on the type of surgery (whether a bone metastasis was completely or incompletely removed).

Table 1. Study cohort characteristics

Category		Number (total n = 39)
Gender	Female	17 (44%)
	Male	22 (56%)
Age (years)	Mean	60
	Range	35-82
Follow up (months)	Median	6.4
	Range	4-10
Race/Ethnicity	Asian	2 (5%)
	Black	3 (8%)
	Hispanic	5 (13%)
	White	29 (74%)
Location of Surgery		
Arm (n = 8)		
	Proximal Humerus	5 (13%)
	Shaft Humerus	2 (5%)
	Distal Humerus	1 (2%)
Leg (n = 31)		
	Pelvis	3 (8%)
	Acetabulum	1 (3%)
	Proximal Femur	20 (51%)
	Shaft Femur	6 (15%)
	Proximal Tibia	1 (3%)
Bone Metastasis Distribution		
	Solitary (No other organ involvement)	5 (13%)
	Solitary Bone Metastasis (with other organ involvement)	23 (59%)
	Multiple Bone Metastases	11 (28%)

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2 Materials/patients and methods

Patients that had surgery for bone metastasis from colorectal carcinoma between 1975 and 2011 at a single institution were retrospectively reviewed. The study included review of medical records and diagnostic data and was approved by the Institutional Review Board. There were 41 patients that had surgery for bone metastases. Two patients were excluded who had surgery for spinal metastases. The study population was composed of 17 females and 22 males (Table 1). For the patient cohort, median age at surgery was 63 years (mean 60; range 35-82). The indications for surgery included intractable pain, the presence of a pathologic fracture, and/or impending pathologic fracture. There were 2 Asian, 3 black, 5 Hispanic, and 29 white patients. Thirty nine patients underwent operative intervention at 8 different appendicular skeletal sites. At the time of skeletal surgery, 23 patients (59%) had a metastasis involving only one bone with additional metastases in organs; and, eleven patients (26%) had additional synchronous bone metastases in more than one bone. Of the 23 patients with single bone involvement and synchronous organ metastases, the most common sites of synchronous metastasis were the lung, liver, and lymph nodes (Figure 1). Five patients (15%) had metastasis in a single bone and no other distant disease in bone or other organs.

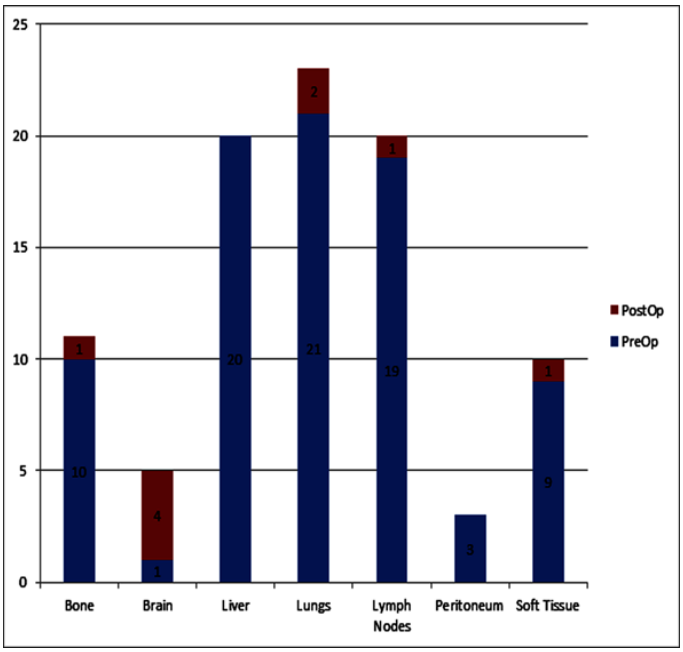

Figure 1. Distribution of metastases pre- and post-op

The minimum patient follow-up was 8 months. At the time of last follow-up, 4 of the 39 patients were living. The cause of all deaths was disease progression. Both patient records and the Social Security Death Index were used to verify the date and cause of death. In Table 2, the surgical procedure characteristics are summarized. For 29 cases, the bone metastasis was completely removed (28 of 29 are shown in Table 2 — the excluded patient did not have EBL data available). For the remaining 10 cases (8 patients with EBL data available shown in Table 2), the bone was stabilized without removing the tumor. The bone surgical site was treated preoperatively with radiation in twelve patients; and postoperatively in eleven patients.

For surgeries where the BM was resected, the mean blood loss was 920 mL (range 50-6500 mL, n = 28). The blood loss in the surgeries that did not include BM removal was not statistically different (mean = 343 mL, range 0-600 mL, n = 8). No intraoperative deaths occurred for the patient cohort.

Kaplan-Meier curves were determined for overall survival and progression free survival at the bone surgery site. Survival curves for different groups were compared using the log rank test. Recurrence was determined from serial imaging of the bone surgery site, and was defined as the reappearance of osseous or soft tissue tumor after the initial surgery to remove

the bone metastasis. The student's t-test was used to compare means. The Wilcoxon rank-sum test was used to evaluate the association of blood loss volume with bone metastasis resection. Statistical analysis was perfmed using the SAS version 9.2 and S-Plus version 8.0 software programs. Statistical significance was defined as $p < 0.05$.

Table 2. Surgery characteristics

	Estimated blood loss (EBL)*	Procedure	Number
Bone stabilization without resection of bone metastasis 8 Cases	Mean 344 cc Range 0-600 cc	Intramedullary fixation (Closed)	5
		Plate fixation	1
		Biopsy only/no fixation	2
		Total	8
Bone metastasis resection 28 Cases	Mean 920 cc Range 50-6500 cc	Intramedullary fixation + bone cement	5
		Intramedullary fixation	2
		Plate fixation + bone cement	2
		Endoprosthesis	12
		Total Hip Arthroplasty	5
		No reconstruction	2
		Total	28

*EBL was unknown in 3 of 39 cases

3 Results

Patient survival following a diagnosis of colorectal cancer was as follows: 85% -1 year, 22% -5 years, and 14% -10 years; with 3.3 year median survival (Figure 2a). The median time to the first surgery for bone metastasis was 26 months after diagnosis (Figure 2b). After bone metastasis surgery, patient survival was as follows: 30% -1 year, 18% -2 years, and 9%-3 years (median 6.4 months) (Figure 2c). All but 4 patients were deceased at last follow-up. Bone metastasis removal (compared with incomplete removal) (Figure 2d) was associated with a lower risk of death, afteradjusting for age and gender. Median survival after surgery was 8 months if the bone metastasis was removed, and only 3 months in patients who did not have bone metastases excised ($p = 0.014$). Survival was also longer for patients who presented with solitary bone involvement (139 months), compared with multiple bones (4 months), or other synchronous involvement (6 months, $p = 0.023$, Figure 2e). None of the patients with simultaneous additional metastases in other bones at the time of skeletal surgery survived beyond 3 years. Multivariate analysis showed that bone location (upper v. lower extremity), race/ethnicity, chemotherapy, and radiation treatment either pre- or post-operatively, were not significant variables for overall survival.

Four of the 39 patients having surgery subsequently had local recurrence. For these patients, the median time from their first bone metastasis surgery to local disease progression was 19 months (Figure 3a). There were no local recurrences observed after 20 months from surgery. The treatment for local recurrence was additional surgery in all cases. A patient example is shown in Figure 3b-d. For this case, the initial surgery was an intramedullary nail for an impending fracture from a femoral metastasis. This patient developed a local recurrence 12 months after surgery, which was resected, and

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reconstructed with a total femur endoprosthesis (Figure 3b-d). The patient died 12 months later from progression of disease in the brain and lungs.

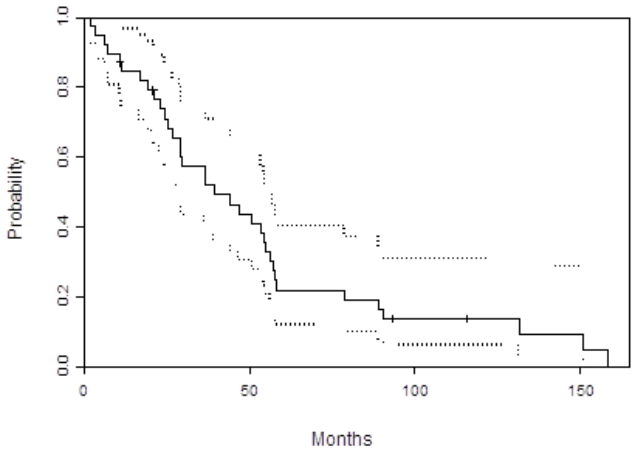

Figure 2a. Overall survival following diagnosis of colon carcinoma

Following the diagnosis of colorectal cancer, overall survival was 85% at 1 year (95% CI 74-97%), 57% at 3 years (95% CI 44-76%), 22% at 5 years (95% CI 12-40%), and 14% at 10 years (95% CI 6-31%)

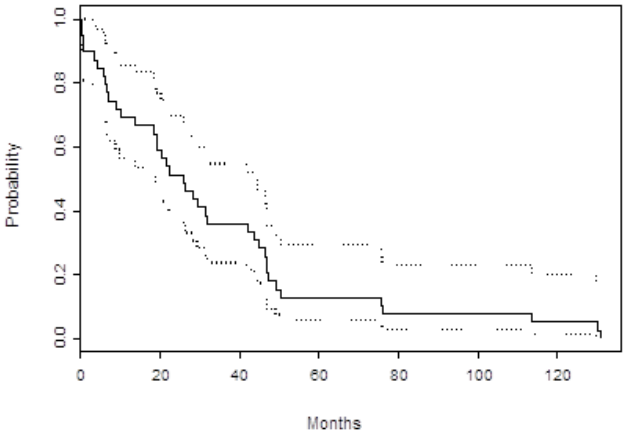

Figure 2b. Time to first surgery for a bone metastasis following diagnosis of colon carcinoma

The time to the initial surgery for a bone metastasis following colon cancer diagnosis is shown. The median time was 26 months (95% CI 19-44%).

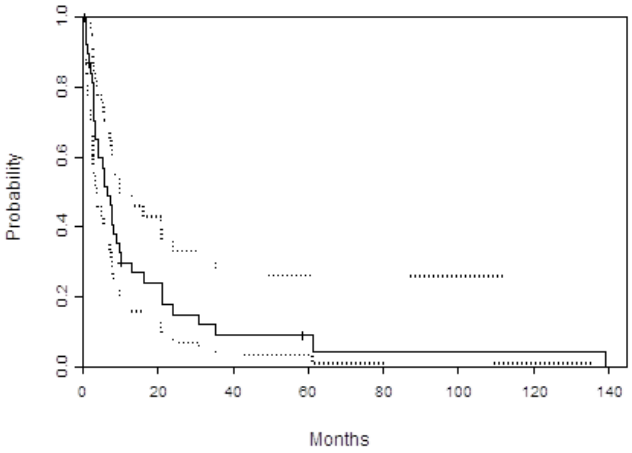

Figure 2c. Overall survival after bone metastasis surgery

Following surgery for a bone metastasis, overall survival was 30% at 1 year (95% CI 18-49%), 18% at 2 years (95% CI 9-36%), and 9% at 3 years (95% CI 3-26%).

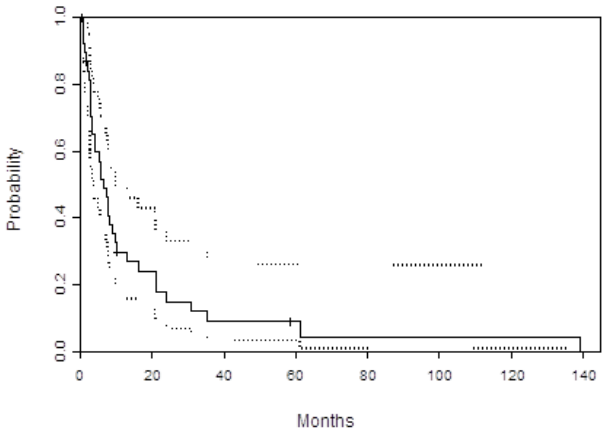

Figure 2d. Overall survival following surgery for bone metastasis. Complete bone metastasis removal was associated with longer survival

The dependency of overall survival on whether the bone metastasis was completely removed vs. not excised. The median survival time after surgery that excised bone metastasis was 8 months (95% CI 4-21 months), compared with 3 months (95% CI 1-8 months) for surgery that did not include bone metastasis excision (p = 0.014). None of the patients that had non-excisional surgery survived beyond 16 months.

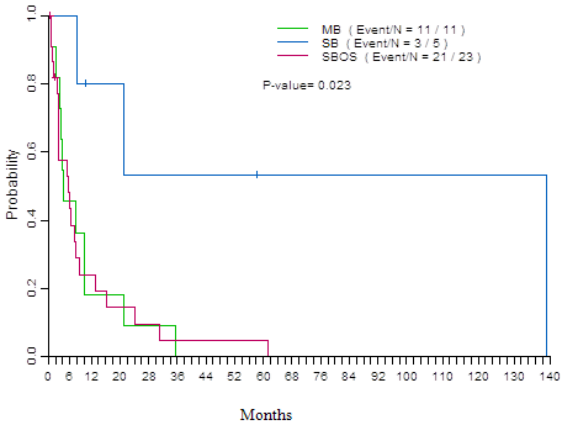

Figure 2e. Overall survival following surgery for bone metastasis. Patients with an isolated metastasis in a single bone (SB) had longer survival

Overall survival for patients who had a solitary bone (SB) metastasis (with no other distant metastasis) at the time of skeletal surgery, compared to patients with multiple bone (MB) metastases, and to patients with single bone metastasis and simultaneous metastases at other organ sites (SBOS). The median survival for the SB group was 139 months, compared with 6 months for SBOS, and 4 months for the MB group (p = 0.023).

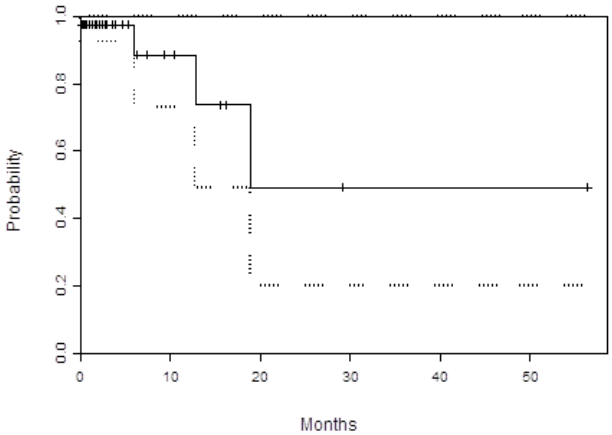

Figure 3a. Time to local recurrence of bone metastasis following surgery

Kaplan-Meier analysis of time to local recurrence in bone following skeletal surgery. The probability of no local recurrence in bone was 97% at 3 months, 89% at 6 months, and 49% at 2 years. There were no local recurrences after 20 months from skeletal surgery.

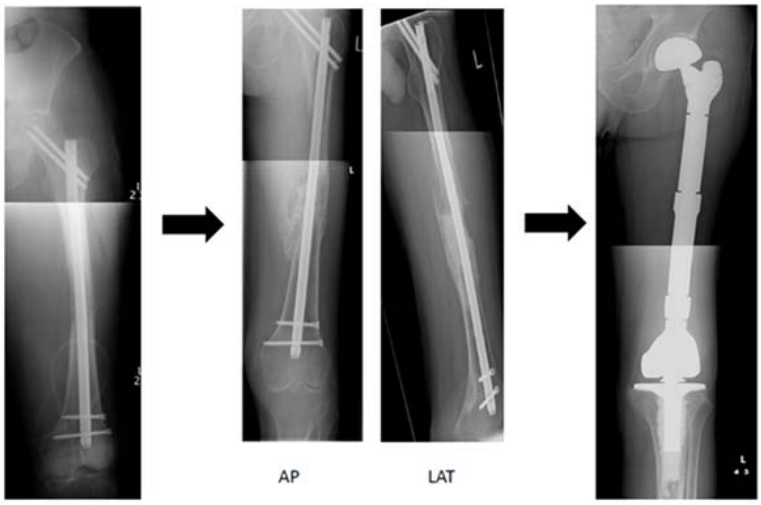

Figure 3b-d. Patient with local recurrence following intramedullary nailing of left femur. Reconstruction was with a total femur endoprosthesis

Figure 3a. Kaplan-Meier analysis of time to local recurrence in bone following skeletal surgery. The probability of no local recurrence in bone was 97% at 3 months, 89% at 6 months, and 49% at 2 years. There were no local recurrences after 20 months from skeletal surgery.

Figure 3b. A patient at risk for a pathologic fracture of the femoral shaft from a colorectal carcinoma metastasis underwent intramedullary nailing with curettage to remove the bone metastasis. Plain X-rays after surgery show a static locked intramedullary nail.

Figure 3c. Twelve months after surgery, the X-ray shows destructive changes in the femur in both AP and lateral projections, consistent with local progression of metastastic disease.

Figure 3d. The postoperative X-ray after revision surgery to remove diseased bone, showing the reconstruction with a total femur endoprosthesis. The remaining femurand hardware were completely resected. The total femur endoprosthesis remained stable for 12 months until the patient died from brain and lung metastatic disease.

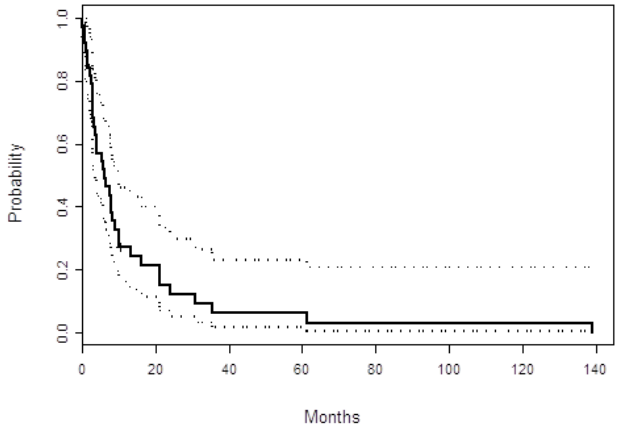

Figure 4a. Recurrence free survival following bone metastasis surgery

The median RFS was 6 months following bone metastasis surgery. The probability of no recurrence or death was 49% at 6 months (95% CI 35-68), 27% at 1 year (95% CI 16-46), 15% at 2 years (95% CI 7-33), and 6% at 3 years (95% CI 2-23).

Kaplan-Meier analysis (Figure 4) of recurrence free survival (RFS) following surgery for skeletal metastasis showed the following patient survival rates: 27% -1 year, 15% -2 years, and 6%-3 years (Figure 4a). Patients treated with preoperative external radiation trended towards a better outcome, although not statistically significant (p = 0.124, Figure 4b). For patients who did not have the bone metastasis removed during surgery RFS was worse (Figure 4c, p = 0.033). Postoperative radiation to the affected bone, multiple versus single bone metastasis involvement, and bone region (upper v. lower extremity), were not significant variables for RFS following bone metastasis surgery.

Five patients had perioperative complications (deep venous thrombosis; respiratory insufficiency; upper GI bleed; pulmonary embolus; wound hematoma). All of these patients recovered without further complications. There were no wound infections, non-unions, hardware failures, or perioperative deaths.

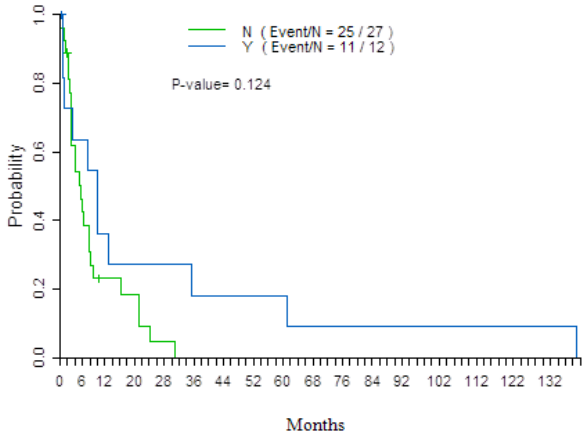

Figure 4b. Time to recurrence or death following surgery for bone metastasis — dependence on pre-operative radiation treatment

The dependence of RFS on preoperative external beam radiation. Administration of external radiation to the site of bone metastasis prior to skeletal surgery tended to improve RFS, but the effect was not statistically significant (p = 0.124).

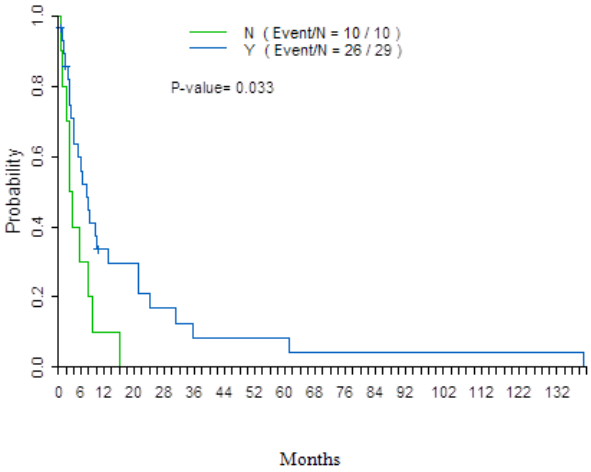

Figure 4c. Time to recurrence or death following surgery for bone metastasis—dependence on complete removal of bone metastasis

The dependence of RFS on resection of the bone metastasis. There was a higher probability of RFS for excisional surgery compared with surgery where the bone metastasis was not excised (p = 0.033). All patients died (n = 10) by 16 months postoperatively if the bone metastasis was not excised.

4 Discussion

As the prognosis for colorectal cancer patients improves, it will be important to assess the functional outcome from surgical intervention for establishing treatment indications and guidelines. Surgery for BM in colorectal cancer is extremely rare and consequently has been infrequently studied. Over 36 years, only 41 patients at our institution, out of a total of 35,543 cases of colorectal carcinoma (0.1%), required surgery for skeletal metastases. Our patient numbers and proportions agree with clinical series reported by others [4, 5, 10, 12, 13, 15-17, 22]. Consequently, prognostic factors following surgery for bone metastases are not well understood.

We acknowledge several limitations of this study. It is a retrospective review of the patients treated at a single institution. Because of the need for surgery was rare, we can report only on a small number of patients, without identically matched cohorts for comparison. The indications for surgery have varied depending on the surgeon and the time period, but overall the decision was either based on symptoms (intractable pain), impending pathologic fracture, and/or a pathologic fracture at presentation. An additional requirement for surgery was that the recovery period was shorter than the life expectancy. It is also difficult to control for changes in surgical technique over the time-period of the study cohort (36 years). Our data are consistent with an improved survival following excisional surgery (rather than stabilization without BM resection), but treatments were not randomized, and followed empirical guidelines. Additionally, different patient groups that might be comparable are not identified. Nevertheless, this study provides insight on treatment methods that may be helpful for surgeons in the decision making process.

The disease free interval from primary colorectal diagnosis to the onset of bone metastasis in this study (median of 26 months) is comparable to other reported series [15, 16]. The overall incidence of osseous metastases from primary tumors of the gastrointestinal tract has been reported as ranging from 1-10.5 percent [1, 18]. In autopsy cases, the incidence is somewhat higher, ranging from 8.6-23.7 percent [9, 11, 12]. Among these, rectal carcinoma metastasizes more often to bone, with a reported incidence of 3.8 to 10.5 percent [5]. Skeletal metastases usually occur after widespread metastatic disease, and are usually osteolytic or mixed osteolytic/osteoblastic [5, 14, 22]. The most common site in the axial skeleton is the femur [1, 5]. Consistent with this observation, in our study 26 of the 39 patients had a metastasis in the femur. Other frequent sites include the humerus and skull [5, 14].

Skeletal metastases are often associated with synchronous disease of the liver and lungs, making isolated skeletal metastases even more uncommon, at 1-2 percent [14]. The mechanism is thought to be primarily via either the venous plexus/IVC, lymphatic chains, or through the portal vein [12]. Metastases to the appendicular skeleton are potentially via the arterial system [5]. Solitary BM have been reported in numerous studies, but a more recent study calls into question whether colon cancer ever metastasizes to bone first. The study by Roth et. al., showed no patients with isolated osseous metastasis at the time of diagnosis [3]. All patients with BM also had metastasis to either liver or lung, as determined by combined PET and CT imaging [3]. In our study, there were 5 patients with solitary BM and no other apparent synchronous metastases. Only 2 of these 5 patients remained alive at most recent follow-up without disease in the liver or lung. One patient had no evidence of disease, and the other had brain and lymph node metastases. All 5 patients had received systemic therapy during their treatment course. Thus, the hypothesis that liver and lung metastases are prerequisite for bone metastases remains questionable and needs further investigation.

The management of osseous metastases usually involves the combined modalities of surgery, chemotherapy, and radiotherapy, and is most often palliative [5]. Our study shows that after surgery for BM, survival is diminished, in agreement with published reports [4-6, 10, 13, 15-17]. Survival beyond 2 years following surgery for BM was rare. But despite limited life expectancy, aggressive surgical removal of BM provided a survival advantage. Patients who underwent conservative surgery without metastasis removal had rapid progression of disease leading to death.

In the patients requiring surgery, skeletal metastases behaved aggressively. Our study findings agreed with observations that survival with metastatic colorectal cancer (median of 3.25 years) is worse than other cancers that more commonly metastasize to bone, such as thyroid, prostate and breast cancers [5, 6, 17, 22]. Patients presented with skeletal metastasis both in the late stages of disease (26 of 39 patients), and with the initial diagnosis (13 of 39 patients). Skeletal surgery occurred at a median of 26 months following the initial diagnosis of colorectal cancer. Only 3 out of 39 patients that had surgery for BM remained alive for more than 8 years following their initial diagnosis.

All local recurrences occurred prior to 20 months after surgery. BM removal was associated with a better recurrence free survival. Local recurrences caused significant morbidity. Indeed, all of the patients (4 in total) with LR underwent additional surgical procedures, resulting in the need for 2 or more surgeries within 2 years on average. Three of the 4 died

from disease progression within 2 years of their initial diagnosis of colorectal cancer. The one remaining patient treated for LR was alive at most recent follow up, with no evidence of disease.

Aggressive surgical treatment of BM has been previously observed to prolong survival and to improve quality of life in patients with metastatic colorectal cancer [14]. In our study, surgical removal of solitary BM was associated with improved survival, in agreement with these observations (Figure 2e). All 5 patients with a solitary and isolated bone metastasis were treated surgically with BM excision. Three of these patients died within 2 years; the remaining 2 were alive at more than 10 years at most recent follow up; suggesting that there are some patients that can be cured of disease by removing the bone metastasis. In those patients with additional bone metastases, the benefit of metastectomy is not clear, with no survival advantage demonstrated in our patients (Figure 2e). Others report similar findings [5, 14].

5 Conclusion

This study showed that following surgery for BM, the only statistically significant indicators for survival and freedom from local disease progression were 1. having undergone excision of the bone metastasis; and 2. presentation with involvement of a single bone and no other distant disease. In patients with multiple bone involvement, bone metastasis excision had a more limited survival advantage, but should be considered to avoid the morbidity of local disease progression, which typically necessitates additional surgery for palliation.

Competing interests

None to report.

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