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Research paper

Retrospective study of predictors of bone metastasis in colorectal cancer patients

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ABSTRACT

Background: We explored risk factors for bone metastasis (BMs) in colorectal cancer (CRC) to improve in early diagnosis and follow-up and to reduce bone metastasis.
Methods: With a retrospective analysis of 2066 patients with CRC treated in our institution from January 2006 to January 2015, we assessed high-risk variables associated with bone metastasis using univariate and multivariate analyses.
Results: Of those subjects studied, 102 patients developed BMs, including 62 of 1014 the rectal cancer patients and 40 of the 1052 colon cancer patients. Lung metastases were accounting for 59.8% of the BMs ($\chi^2 = 17.7$, $p < 0.01$) and hepatic metastases were accounting for 34.3% of BMs ($\chi^2 = 3.06$,$p > 0.05$). BMs were diagnosed more rapidly in the presence of lung metastases(6.9 months versus 11.6 months for liver metastases). Univariate analysis revealed that BMs were associated with primary tumor location ($p < 0.001$), lung metastases ($p < 0.001$), initial stage ($p = 0.001$), radiotherapy ($p < 0.001$) and serum carcinoembryonic antigen (CEA) ($p = 0.001$). Multivariate analysis revealed that primary tumor location (rectum), lung metastases, and serum CEA (> 5 μg/L) were statistically significant ($p < 0.05$).
Conclusions: BMs in rectal cancer occur more frequently than in colon cancer. Lung metastases predicted potential progression to bone in CRCs more than liver metastases. Primary rectal locations, lung metastases and serum CEA were independent risk factors for BMs in CRC. Thus, patients should receive early bones scanning when presenting with CRC.

1. Introduction

Currently, colorectal cancer (CRC) is one of the three most common cancers, with an estimated 1.2 million new cases diagnosed worldwide annually [1]. The incidence of CRC in China ranks third of all malignant tumors and incidence increases every year [2]. CRC metastasizes to the liver and lungs more frequently than to the bone or other organs [3]. Bone metastases (BMs) commonly occur with tumors in breast, lung and prostate, while BMs arising from CRCs are rare, accounting for about 3–5% of BMs [4–6]. Thus, bone scans, X-rays, computed tomography (CT), or magnetic resonance imaging (MRI) are routinely used in CRC patients to identify BMs, which are usually detected when there is bone pain or skeletal-related events (SREs) such as spinal-cord compression, pathological fractures, radio therapy and/or surgery of the bone and hypercalcemia [7–9]. Ho's group [10] reported that bone scans were used routinely in newly diagnosed prostate cancer patients to detect BMs.

Few studies of BMs arising from primary CRC have been published [11]. This, with a single-institution retrospective study, we assessed the relationship between BMs and clinical or pathological variables, including serum CEA at CRC diagnosis. With selective bone scans for high risk CRC patients, we may improve follow-up and BM detection early during the CRC diagnosis.

2. Materials and methods

2.1. Patients

We performed a retrospective analysis of patients with BM originating from CRC who were treated at the Minhang Cancer Hospital Institute, Shanghai, China from January 2006 to January 2015. Of the 2066 patients CRC admitted, 1052 had colon cancer and 1014 had rectal cancer. Patients with BMs (N = 102) were excluded from the study if they had a second primary cancer during follow-up. Table 1

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Table 1
Patients' characteristics in CRC with BMs (n = 102).

Characteristics	n	%
Median age, years (range)	58 y	(22–82)
CEA[a] (μg/l)	27/75	26.5/73.5
< 5/ > 5		
Sex	48/54	47.1/52.9
Female/Male		
PT[a] location	40/62	39.2/60.8
colon /rectal		
PT histology	48	48.1
poorly differentiated medium - high differentiated	54	52.9
Initially Staged		
I~II /III~IV	29 /73	28.4/71.6
Initially treatment		
Surgery	91	89.2
Radiotherapy	38	37.3
Chemotherapy	88	86.3
metastases location		
Lung	61	59.8
Liver	35	34.3

[a] PT primary tumor; carcinoembryonic antigen.

depicts102 patients with BMs data. CRC patients were confirmed to have BMs as follows: reports of bone pain and other SREs; at least one BM identified via a positive bone scan; and identification of BMs by standard X-rays, computed tomography (CT) scans, or magnetic resonance imaging (MRI). Primary tumor site, histological type, and carcinoembryonic antigen (CEA) were noted for all subjects as was initial treatment and location of organ metastasis. The time between primary tumor diagnosis and BMs was recorded. Lymphatic spread and local recurrence were excluded from analysis because most patients had undergone local resection with local lymph node dissection prior to staging work-up. Details appear in Table 1.

2.2. Statistical analysis

Data were assessed with univariate statistical analyses using a Chi-squared test. Multivariate analyses were conducted with a logistic regression model. Statistically significant differences were confirmed with a Student's *t*-test and date that met criteria for ($p < 0.05$) were statistically significant. Average times were expressed as means ± SD. All analyses were performed with SPSS version 17.0. Because we focused on the onset of organ metastasis to bone lesions, we did not perform Kaplan-Meier survival analysis for this study.

3. Results

3.1. Patient clinical characteristics

Over a 9-year period, a total of 2066 patients with primary CRC were treated at the Minhang Cancer Hospital. Single BMs accounted for 9.8% of BMs and 89.2% were multiple-site BMs. BMs most often occurred in the pelvis (35.3%), the lumbar region (25.5%), the thoracic vertebra (21.6%), the sacral vertebral (20.6%), and the rib (14.7%). Other BMs occurred at the shoulder blade (3.4%), the occipital are and skull (2.0% each), and the sternum and cervical vertebra (1.1% each). X-ray, CT, or MRI suggested that 95.1% of patients had osteolytic destruction, and 2.9% had osteoblastic destruction and 2.0% had mixed destruction patterns. Most patients(71.6%) were diagnosed stage of III-IV with bone metastasis at initial diagnoses of CRC(showed in Table 1). At the time of diagnosis of bone metastases, 73.5% (75/102) patients had high levels (> 5 ng/ml) of serum carcinoembryonic antigen (CEA). that was significantly different than normal level was 26.5%(27/102) ($p < 0.05$); In fact, 38 patients had CEA level > 100 ng/ml. In univariate analyses, highlighted that several parameters had a significant influence BMs in CRC, such as the PT location, staging,Radiotherapy and lung metastasis and CEA (shown in Table 2); In multivariate analyses, CEA, primary tumor location(rectum)and lung metastasis were independent risk factors for bone metastasis($p < 0.05$) (showed in Table 3).

Table 2
Patient univariate analyses in CRC with BMs (n = 102).

Characteristics	n	%	χ^2	P
CEA (μg/l)	27/75	(26.5/73.5)	50.122	< 0.001
< 5/ > 5				
Sex	48/54	(47.1/52.9)	0.002	0.962
Female/Male				
PT* location	40/62	(39.2/60.8)	32.596	< 0.001
colon /rectal				
PT histology			2.908	0.101
poorly differentiated medium - high differentiated	48 54	(48.1) (52.9)		
Initially Staged				0.001
I~II /III~IV	29 /73	(28.4/71.6)	13.138	
Initially treatment				
Surgery	91	(89.2)	28.408	0.458
Radiotherapy	38	(37.3)	14.727	< 0.001
Chemotherapy	88	(86.3)	7.682	0.062
metastases location				
Lung	61	59.8	48.690	< 0.001
Liver	35	34.3	1.177	0.279

Table 3
Multivariate analyses in CRC patients with BMs (n = 102).

Risk factors	Regression coefficient	standard error	95%CI	P value
PT location	0.878	0.359	1.190–4.1024	0.015
lung metastasis	0.947	0.360	1.274–5.215	0.008
Initially staged	1.560	0.961	0.723–31.305	0.105
Radiotherapy	0.646	0.418	0.840–4.400	0.123
CEA	1.443	0.350	2.132–8.199	< 0.001

3.2. Characteristics of metastases

Of the 2066 patients, 15.4% had lung metastasis, 44.2%had liver metastasis, and 4.9% had BMs. Only 3 patients had BM with no other organ involvement. Lung and liver metastases occurred in 61 and 35 patients who had BMs, respectively. Table 4 depicts these data. Only 13 of the102 patients developed brain metastases and all were accompanied by lung metastasis during follow-up. Other rare metastasis sites were uterine, annex, bladder, and the abdominal cavity. Lymphatic spread and local recurrence were excluded from analysis because most patients underwent local resection with local lymph node dissection prior to staging work-up.

3.3. Average time to organ metastasis

The average time from initial CRC diagnosis to detection of liver metastases was 12.4 months (± 20.9, CI 9.5–31.5), significantly shorter than the 25.8 months (± 38.7, CI 20.3–37.2) for detecting lung

Table 4
Colorectal cancer organ metastases.

Organ metastasis n1 = 2066	(%) n2 = 102	(%)
liver 319	(44.2) 35	(34.3%)
lung 914	(15.4) 61	(59.8%)

Table 5
Progress time to organ metastasis in CRC.

Type of Metastasis	average time (m)	Patients (n)
from liver to bone metastasis	11.6 ± 11.1	35
from lung to bone metastasis	6.9 ± 5.6	61
from bone to brain metastasis	4.1 ± 3.3	13

metastases and 29.6 months (± 36.8, CI 18.0–37.9) for identifying BMs ($p < 0.05$). Table 5 describes the average time of CRC patients with liver and/(or) lung metastases from diagnosis to confirmation of BMs. These differences were not statistically significant ($p > 0.05$). Of those CRC patients studied, 13 had brain metastases that were accompanied by lung metastases and 3 patients had tumors in the liver, lung, brain, and bone.

4. Discussion

Because BMs are usually identified by bone pain and SREs that reduce quality of life, understanding how CRC produces BMs is essential. This retrospective study was conducted to assess characteristics of CRC patients with BMs to improve BM detection earlier and to improve patient quality of life.

According to the literature [12,13], BMs in patients with CRC is extremely rare, the incidence of CRC with BM is 0.96–11.1% and BMs tend to suggest poor prognosis. Roth's group [14] retrospectively analysed clinical data from 252 patients with CRC and reported that 5.5% had BMs identified during the first visit. Another study suggested that the incidence of CRC and BM was approximately about 4.5% [15]. In our study of 102 patients with CRC, approximately 4.9% had BM, and this agreed with reports in the literature.

Approximately 6.1% of patients with rectal cancer had BM and this exceeded the 3.8% of patients with colon cancer and BMs ($\chi^2 = 4.45$, $p < 0.05$). These data were similar to reports in the literature to suggested that 8.9% of rectal cancer patients had BMs and 5.1% of colon cancer patients had BMs [16]. Diagnostic circumstances and study types appear to affect reported data and one of these being tumor site. Studies show that [17,18] more BMs occur in rectal cancers compared to colon cancers which may be influenced by the vasculature surrounding rectal tumors.

Medium-high differentiated adenocarcinoma patients accounted for 52.9% of the 102 cases of BMs and 47.1% poorly differentiated ($\chi^2 = 3.02$, $p > 0.05$). It was not statistically significantly different. Patients with clinical CRC stages of I–II at the first clinical visit accounted for 28.4% of BMs and patients with CRCs at III–IV stages at the first clinical visit accounted for 71.6% of BMs ($\chi^2 = 6.93$, $p < 0.01$). Thus, BMs in CRC are correlated to clinical stage at the first visit rather than the pathological degree of differentiation(in Table 1). But III–IV stage disease at the first clinical visit was not independent risk factor in CRC patients with BM by multivariate analyses ($P = 0.105$).

In our study, primary rectal locations, lung metastases and serum CEA were independent risk factors for in CRC. In our study, 73.5% of patients had high CEA and these values were statistically significantly different than those compared to patients(26.5%) who had normal CEA ($p < 0.05$). Thus, patients with lung metastases and high CEA should be monitored for BM especially for CEA values exceeding > 100 μg/L. Our results (showed in Table 3)were similar to the literature reported by Li A, et al. [19]. They found three independent risk factors, namely rectal cancer, lymph node metastasis (LN) and pulmonary metastasis (PM) for developing a scoring system to predict bone metastasis after radical resection within 5 years. It remind us that factors (especially for rectal locations, lung metastases)could help clinicians to identify patients at risk for continuous monitoring and optimize surveillance to be able to detect and treat bone metastases very early in order to avoid skeletal complications.

Single-site BMs accounted for 9.8% of those detected in our sample and the rest were multiple-site BMs. BMs most frequently occurred in the pelvis (35.3%). Bone-exclusive metastases occurred in 0.98% of CRC patients and this agrees with data from Kanthan's group [16] who reported that 1.1% of CRC patients developed isolated metastasis. Thus, BMs without other organ involvement for CRC patients is rare.

Our results show that BMs were identified in CRC patients later than that reported by Santini's group [11]. This might be explained by differences in primary tumor stages between the studied populations. We found that lung metastasis occurred with BMs most frequently. Thus, lung metastases may be predictive of future BMs in this patient group. Zhang, et al. suggested that [18] BMs may arise from the inferior vena cava and proceed directly into the pulmonary circulation

Our data regarding time to BM detection given lung or liver metastases suggests that lung metastases are more serious indicators than hepatic metastases. Chambers reported that [20] CRC metastasizes first to the liver or lungs, which both contain dense capillary beds that can trap tumor cells and seed them into other organs. BMs were diagnosed more rapidly in the presence of lung metastases(6.9 months vs. 11.6 months for liver metastases)

We also noted that brain metastasis occurred in 12.7% of patients and that these brain metastases took about 4.1 months to identify and that lung metastases co-occurred with them. Thus, lung metastases may predict future brain metastases and may predict poorer prognosis. These data are aligned with those of Sundermeyer, et al. [21] that bone metastases are usually signs of poor prognoses. As Elisabeths' group reported [22], median survival time were about 114 days after bone metastasis only and 79 days after bone with additional organ metastases in patients with rectal cancer (95% CI 1.06–2.05). While the data were 105 days and 95 days in patients with colon cancer(95% CI 1.02–1.87),respectively. Furthermore, it might remind us that additional organ metastases might be indicative of a more aggressive prognosis than bone metastasis only.

Our study was a single-center retrospective analysis and as such is limited. Still, our data offer valuable tools for identifying CRC patients who are likely to develop BMs. These patients may benefit from early screening which may help with clinical decision-making that could prolong life.

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Notes

The author has no financial conflicts of interest.

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