

A Scoring System to Predict the Development of Bone Metastasis After Radical Resection of Colorectal Cancer

ANG LI^{1*}, LUKAS KÄSMANN^{2,3*}, DIRK RADES³ and CHUANGANG FU^{1,2}

¹Department of Colorectal Surgery, Changhai Hospital,

The Second Military Medical University, Shanghai, P.R. China;

²Department of Colorectal Surgery, Shanghai East Hospital, Tongji University, Shanghai, P.R. China;

³Department of Radiation Oncology, University of Lübeck, Lübeck, Germany

Abstract. *Background/Aim:* To develop a scoring system to predict bone metastasis after radical resection within 5 years. *Patients and Methods:* We evaluated the patient records of 1,749 patients, of whom 50 patients developed bone metastasis. *Treatment-related factors (age, gender, localization, histology, preoperative carbohydrate antigen 199 level, T-stage, lymph node metastasis (LN) and pulmonary metastasis (PM)) were analyzed. Results:* We found three independent risk factors, namely rectal cancer ($p=0.038$), LN ($p=0.006$) and metachronous PM ($p<0.001$). *Scoring was conducted by adding zero or one point from each variable and resulted in four groups of 0, 1, 2 or 3 points. Three groups were formed, with 0-1 points vs. 2 points vs. 3 points (1.5% vs. 6.6% and 10.5%, $p<0.001$). Conclusion:* This new score can help clinicians 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.

Colorectal cancer is the third most common type of cancer and a major contributor to cancer-related mortality worldwide (1-3). In early stages, modern treatments including the latest chemotherapy and radiotherapy regimens can achieve 5-year-survival rates of 80-100% with acceptable toxicity and avoidance of the loss of gastrointestinal function (1, 4). Moreover, surgery is an important component of colorectal treatment, neoadjuvant

radiochemotherapy offers tumor downsizing and prevention of disease recurrence (4). Adjuvant chemotherapy may prevent recurrence while improving survival (3), but only selected patients benefit while latest and ongoing studies try to reveal who responds to what kind of chemotherapy (5). Nevertheless, surgery is the most important local treatment and operative procedure has evolved in the past years (6, 7) lowering local recurrence rate and survival prolongation.

Prognostic factors are needed to identify patients at risk and to optimize treatment. Several factors have been suggested to have an impact on the outcome in terms of survival or locoregional recurrence such as DDR2 expression, phosphoserine phosphatase, preoperative total lesion glycolysis (TLG), nutritional status and lower body mass index (8-14). These factors can help to understand a patient's prognosis and optimize treatment allocation.

The development of bone metastasis after complete resection of colorectal cancer is a severe event for patients and the treating physicians. Survival and mobility are often limited in these patients and the quality of life is low. The overall survival of these patients ranges between 3-12 months and treatment options are limited. Several scorings systems were developed to predict survival and mobility (15-17) to guide physicians and optimize treatment.

We aimed to develop a scoring system to predict the occurrence of bone metastasis after radical resection of colorectal cancer in order to identify patients at risk and contribute to colorectal surveillance management.

Patients and Methods

Between January 2001 and December 2010, 1749 patients with colorectal cancer received radical surgery in the Department of Colorectal Surgery, Shanghai Hospital of The Second Military Medical University, Shanghai, P.R. China. These patients were followed-up for five years and 50 patients developed bone metastasis.

In Table I, the data of the patients with metachronous bone metastasis are displayed.

*These Authors contributed equally to this study.

Correspondence to: Chuangang Fu, Department of Colorectal Surgery, Shanghai East Hospital, Tongji University, Shanghai, P.R. China. Tel: +86 02131166666, e-mail: fugang416@126.com

Key Words: Colorectal cancer, predictive factors, surgery, bone metastasis, score.

Inclusion criteria: 1. Postoperative pathology examination showed adenocarcinoma or mucinous adenocarcinoma. 2. All patients had received radical surgery with negative resection margin (R0).

Exclusion criteria: 1. Patients with distant metastasis or primary cancer in another organ at diagnosis were excluded. 2. Patients with local recurrence after operation were excluded.

Treatment. Treatment allocation was according to the treatment guidelines of the National Comprehensive Cancer Network (NCCN, USA). All patients underwent resection of the primary tumor with adequate margins, which was evaluated postoperatively by pathologists. Rectal cancer patients were treated according to their disease stage and underwent total mesorectal excision (TME). Stage III patients usually received preoperative neoadjuvant chemoradiotherapy if they did not disagree to preoperative treatment.

Patients with stage II or a more advanced stage of colorectal cancer had received a 5-Fu based chemotherapy postoperatively as a common adjuvant chemotherapy.

Potential prognostic factors. Eight factors including age (<60 vs. ≥60 years), gender, tumor site (rectum vs. colon), histology (adenocarcinoma vs. mucinous adenocarcinoma), T-category (T1-2 vs. T3-4), Lymph node metastasis (positive vs. negative), Preoperative C199 levels (<37 kU/L vs. >37 kU/L) and metachronous pulmonary metastasis (yes vs. no) were evaluated.

Statistical analyses. Univariate analysis was performed using Chi square test to reveal an association with the metachronous bone metastasis of colorectal cancer. Significant factors ($p < 0.05$) were consequently included in a logistic multivariate analysis. Scoring was conducted by adding one point for having the independent factor and zero for not having from each variable (Table II). Three risk groups were formed. Differences between the risk groups were evaluated with the Kaplan–Meier method (18) and calculated with log-rank test (univariate analysis).

Results

Patients who developed metachronous bone metastasis were evaluated and their characteristics are displayed in Table I. In Univariate analysis, tumor site ($\chi^2=4.932, p=0.026$), preoperative carbohydrate antigen 199 (CA199) level ($\chi^2=4.266, p=0.039$), lymph node metastasis ($\chi^2=13.054, p=0.000$) and pulmonary metastasis ($\chi^2=35.524, p=0.000$) were associated with metachronous bone metastasis. These factors were evaluated in logistic multivariate analysis and three independent risk factors remained: namely rectal cancer (odds ratio (OR)=0.508, 95%CI=0.268-0.963, $p=0.038$), lymph node metastasis (OR=2.291, 95%CI=1.273 to 4.122, $p=0.006$) and metachronous pulmonary metastasis (OR=4.796, 95%CI=2.473 to 9.301, $p < 0.001$).

Scoring resulted in four groups of 0, 1, 2 or 3 points with bone metastasis occurrence rates of 0.81%, 1.96%, 6.6% and 10.5% in the whole patient collective. Three risk groups were formed (see Figure 1) with 0-1 points vs. 2 points vs. 3 points (1.5% vs. 6.6% and 10.5%, $p < 0.001$).

Table I. Patient characteristics.

	Number of patients	Proportion (%)
Age		
<60 years	22	44
≥60 years	28	56
Gender		
Female	21	42
Male	29	58
Tumor site		
Rectum	36	72
Colon	14	28
Histology		
adenocarcinoma	43	86
mucinous adenocarcinoma	7	14
T-category		
1-2	8	16
3-4	42	84
Lymph node metastasis		
Negative	20	40
Positive	30	60
Preoperative C199 levels		
<37 kU/L	38	76
>37 kU/L	12	24
Metachronous pulmonary metastasis		
Yes	14	28
No	36	72

Table II. Scoring system.

	Points
Tumor site	
Rectum	1
Colon	0
Lymph node metastasis	
Positive	1
Negative	0
Metachronous pulmonary metastasis	
Yes	1
No	0

Discussion

Colorectal cancer remains the third most common type of cancer and a major cause of cancer-related death worldwide (1-3), but the outcomes in terms of survival, locoregional control and metastases free-survival for colorectal cancer have dramatically improved in the last decade due to treatment improvements (1, 4, 6). The development of screening tests and their nationwide use leads to early diagnosis in lower disease stages and higher survival rates.

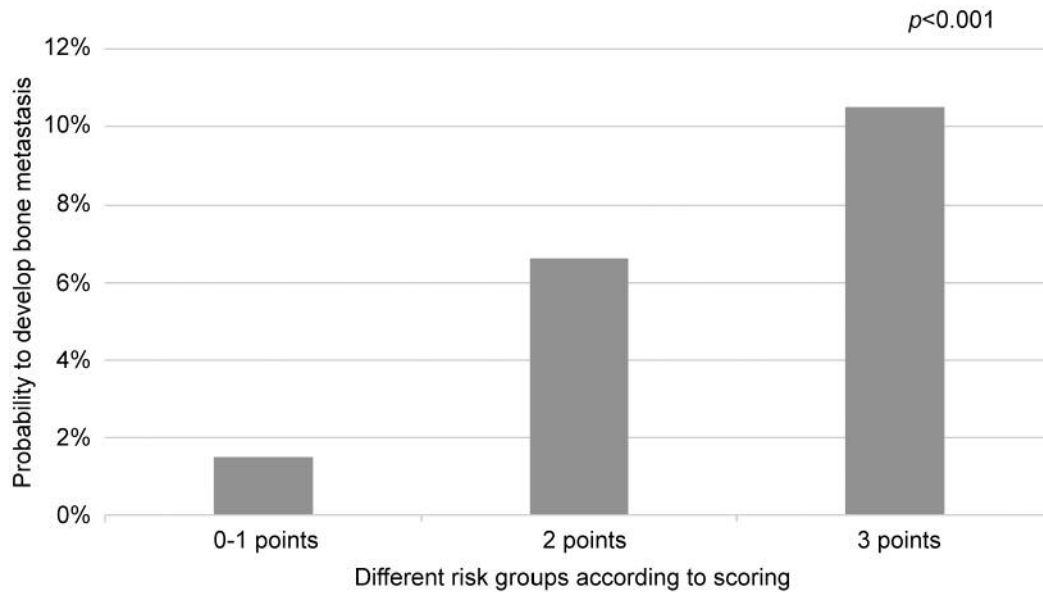


Figure 1. Three risk groups of developing bone metastasis after surgery.

The increase in overall survival (OS) of colorectal cancer patients may increase the likelihood of bone metastasis during the course of the disease (18). Future studies should develop a better surveillance management for these patients to detect metastasis early and find their optimal treatment allocation (1).

The development of bone metastases represents a crucial burden for cancer patients suffering from bone pain, loss of mobility, pathological fractures or spinal cord compression. Several studies investigated the survival and mobility after metastasis of colorectal cancer and developed survival and mobility scores (15, 17, 18).

Only a few studies investigated risk factors for the occurrence of bone metastasis for colorectal cancer (19, 20). Sun *et al.* evaluated 516 patients who underwent curative resection for colorectal cancer and found two independent risk factors namely tumor location and lymph node involvement (19). In a larger study, we confirmed this findings and found metachronous pulmonary metastases to be a third independent risk factor (20). In this study, we developed the first score for the occurrence of bone metastasis after radical resection based on three different risk groups (see Figure 1). Scoring was conducted by adding one point for having the independent factor and zero for not having from each variable. With this predictive instrument physicians can estimate patients' risk and improve their surveillance management.

Treatment options for bone metastasis are limited, but surgery, radiotherapy and bisphosphonate appear to be

effective and in some cases even curative treatment is possible. Immunotherapies are emerging and new antibodies with bone-modifying ability *e.g.* denosumab have been shown to prevent skeletal complications in patients with bone metastasis. However, prophylactic treatment with bisphosphonate or denosumab causes severe side effects and should be questioned in routine use. We found an occurrence rate of bone metastasis in the high-risk group of over 10%. Even in this situation the prophylactic usage of bisphosphonate or denosumab should be highly questioned and only an individual's decision.

When interpreting these results, the retrospective nature of the data and a long recruiting time of patients should be considered. Besides, prospective studies regarding risk factors for the development of bone metastasis after radical surgery of colorectal cancer are not available.

We are convinced that the developed score helps physicians to identify patients at risk and to improve surveillance management for high-risk patients and decrease skeletal events in these patients.

Conclusion

In summary, this new score can help clinicians identify patients at risk for continuous monitoring and optimize surveillance management for patients to detect and treat the bone metastases very early in order to avoid the occurrence of skeletal complications.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

Acknowledgements

The Authors would like to thank Brian Matthew Buh (Iowa, USA) for proof-reading and editing suggestions.

References

- 1 van der Stok EP, Spaander MC, Grünhagen DJ, Verhoef C and Kuipers EJ: Surveillance after curative treatment for colorectal cancer. *Nat Rev Clin Oncol* 14: 297-315, 2017.
- 2 Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson AB, Mariotto A, Lake AJ, Wilson R and Sherman RL: Annual report to the nation on the status of cancer, 1975-2014, featuring survival. *JNCI J Natl Cancer Inst* 109(9): djx030, 2017.
- 3 Ando K, Oki E, Saeki H, Kasagi Y, Tsuda Y, Zaito Y, Nakashima Y, Imamura Y, Ohgaki K and Maehara Y: Number of lymph node metastases may indicate the regimen for adjuvant chemotherapy in patients with stage III colorectal cancer. *Anticancer Res* 35: 6207-6211, 2015.
- 4 Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E and Hess CF: Preoperative *versus* postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351: 1731-1740, 2004.
- 5 Yi WB, Um JW, Ryu JS, Hong KD, Kim JS, Min BW, Jung SY, Lee JH and Kim YS: Clinical significance of 5-fluorouracil chemosensitivity testing in patients with colorectal cancer. *Anticancer Res* 37: 2679-2682, 2017.
- 6 Dayal S, Battersby N and Cecil T: Evolution of surgical treatment for rectal cancer: a review. *J Gastrointest Surg* 21: 1166, 2017.
- 7 Kawahara H, Misawa T, Watanabe K, Hojo S, Ishida K, Akiba T and Yanaga K: Feasibility of single-incision laparoscopic surgery plus one assist port for anterior resection. *Anticancer Res* 36: 467-469, 2016.
- 8 Yiu AJ and Yiu CY: Biomarkers in colorectal cancer. *Anticancer Res* 36: 1093-1102, 2016.
- 9 Sasaki S, Ueda M, Iguchi T, Kaneko M, Nakayama H, Watanabe T, Sakamoto A and Mimori K: DDR2 Expression is associated with a high frequency of peritoneal dissemination and poor prognosis in colorectal cancer. *Anticancer Res* 37: 2587-2591, 2017.
- 10 Sato K, Masuda T, Hu Q, Tobo T, Kidogami S, Ogawa Y, Saito T, Nambara S, Komatsu H and Hirata H: Phosphoserine phosphatase is a novel prognostic biomarker on chromosome 7 in colorectal cancer. *Anticancer Res* 37: 2365-2371, 2017.
- 11 Uratani R, Toiyama Y, Shimura T, Mori K, Fujikawa H, Hiro J, Ohi M, Inoue Y, Tanaka K and Araki T: Preoperative lower body mass index correlates with poorer prognosis in patients undergoing curative laparoscopic surgery for colorectal cancer. *Anticancer Res* 35: 5639-5648, 2015.
- 12 Nagata T, Nakase Y, Nakamura K, Sougawa A, Mochiduki S, Kitai S and Inaba S: Prognostic impact of a nutritional index including muscle volume in stage 4 colorectal cancer. *In Vivo* 30: 885-891, 2016.
- 13 Shibutani M, Maeda K, Nagahara H, Iseki Y, Ikeya T and Hirakawa K: Prognostic significance of the preoperative ratio of C-reactive protein to albumin in patients with colorectal cancer. *Anticancer Res* 36: 995-1001, 2016.
- 14 Ogawa S, Itabashi M, Kondo C, Momose M, Sakai S and Kameoka S: Prognostic value of total lesion glycolysis measured by ¹⁸F-FDG-PET/CT in patients with colorectal cancer. *Anticancer Res* 35: 3495-3500, 2015.
- 15 Rades D, Bartscht T, Janssen S, Bajrovic A, Segedin B and Schild SE: Forecasting survival probabilities after radiotherapy of metastatic epidural spinal cord compression from colorectal cancer in the elderly. *Anticancer Res* 36: 1829-1833, 2016.
- 16 Rades D, Dahlke M, Gebauer N, Bartscht T, Hornung D, Trang NT, Phuong PC, Khoa MT and Gliemroth J: A new predictive tool for optimization of the treatment of brain metastases from colorectal cancer after stereotactic radiosurgery. *Anticancer Res* 35: 5515-5518, 2015.
- 17 Zhang W-Y, Li H-F, Su M, Lin R-F, Chen X-X, Zhang P and Zou C-L: A simple scoring system predicting the survival time of patients with bone metastases after RT. *PloS One* 11: e0159506, 2016.
- 18 Liu F, Zhao J, Xie J, Xie L, Zhu J, Cai S, Zheng H and Xu Y: Prognostic risk factors in patients with bone metastasis from colorectal cancer. *Tumor Biol* 37: 16127, 2016.
- 19 Sun C, Deng Y, Zhou H and Hu ZQ: Risk factors for the development of metachronous bone metastasis in colorectal cancer patients after curative resection. *Int J Surg* 21: 145-149, 2015.
- 20 Li A, Tan Z, Fu C, Wang H and Yuan J: Analysis of risk factors for bone metastasis after radical resection of colorectal cancer within 5 years. *Zhonghua Wei Chang Wai Ke Za Zhi* 20: 58-61, 2017.

Received July 2, 2017
 Revised July 14, 2017
 Accepted July 17, 2017