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Cutaneous Metastases in Colorectal Cancer

Kolorektal Kanserde Cilt Metastazları

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Objectives: Cutaneous metastases of colorectal cancer are rarely detected in clinical practice. This study aimed to evaluate the patients with cutaneous metastases of colorectal cancer in order to define their clinical presentation, clinical course, and prognosis.

Patients and Methods: Patients (7 females, 1 male; mean age 49 years; range 28 to 72 years) treated for colorectal cancer and who developed cutaneous metastases during follow-up were evaluated. Patients' demographic characteristics, location of the primary tumor and cutaneous metastases, histopathologic properties and stage of the primary tumor, location of accompanying metastases, and treatment methods were recorded.

Results: All patients had stage III colorectal cancer and were treated with adjuvant chemotherapy. Cutaneous metastases appeared in a mean duration of 25 months after surgery and were located in the anterior abdominal wall and presacral region. Following cutaneous metastases, seven patients died whereas one patient is alive after 63 months. Mean survival time after cutaneous metastases was 17 months. Four patients survived more than four years from the time of surgery, one of which had only cutaneous metastases.

Conclusion: In colorectal cancer patients, suspicious looking skin lesions should be excised as early as possible to increase the detection rate of patients with isolated cutaneous metastases.

Key words: Colorectal cancer; cutaneous metastases; prognosis.

Amaç: Kolorektal kanserin cilt metastazlarıyla klinik uygulamada nadiren karşılaşılır. Bu çalışmada, kolorektal kanserli ve cilt metastazı olan hastaların hastalığın ortaya çıkış bulguları, seyri ve prognozu açışından değerlendirilmesi amaçlanmıştır.

Hastalar ve Yöntemler: Kolorektal kanser tanısıyla tedavi edilen ve takiplerinde cilt metastazı gelişen hastalar (7 kadın, 1 erkek; ort. yaş 49; dağılım 28-72) değerlendirildi. Hastaların demografik özellikleri, primer tümör ve cilt metastazlarının yeri, primer tümörün histopatolojik özellikleri ve evresi, eşlik eden diğer metastazların yeri ve tedavi yöntemleri incelendi.

Bulgular: Hastaların tümünde evre III kolorektal kanser mevcuttu ve adjuvan kemoterapi ile tedavi edildi. Cilt metastazları cerrahiden ortalama 25 ay sonra ortaya çıktı ve karın ön duvarı ile presakral bölgede yerleşmişti. Cilt metastazlarından sonra takipte yedi hasta ölürken bir hasta 63 aydır sağdır. Cilt metastazlarından sonra ortalama sağkalım süresi 17 aydır. Birinde sadece cilt metastazı olan dört hasta cerrahiden sonra dört yıldan daha fazla yaşamıştır.

Sonuç: Kolorektal kanserli hastalarda, şüpheli cilt lezyonları mümkün olduğu kadar erken eksize edilerek sadece cilt metastazı olan hastaların saptanma oranı artırılmalıdır.

Anahtar sözcükler: Kolorektal kanser; cilt metastazı; prognoz.

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Cutaneous metastases are rarely encountered in cancer patients with an incidence of 0.9-8% in various cancer types whereas those originating from internal malignancies have a similar rate (0.7-9%).[1-3] Besides, cutaneous metastases from colorectal cancer comprise approximately 5% of all cutaneous metastases.[1,4] Although cutaneous metastases of colorectal cancer are rarely seen, they sometimes can be the first sign of disease recurrence with a better prognosis. For this reason, it is important to gather information on the clinical presentation, therapeutic options, and prognosis of the patients with cutaneous metastases. Previous studies evaluating this group of patients are either case reports or autopsy series. In this study, a group of patients with cutaneous metastases of colorectal cancer was prospectively evaluated to gain a better insight to their clinical presentation, clinical course, and prognosis.

PATIENTS AND METHODS

Patients diagnosed as colorectal cancer between 2003 and 2006 and treated with a curative intent and who developed cutaneous metastases during follow-up were included in this study. Two hundred and sixty three patients were treated for colorectal cancer during the study period. Eight patients (3%; 7 females, 1 male; mean age 49 years; range 28 to 72 years) with cutaneous metastases of colorectal cancer were included in this study. Those patients with distant metastases at the time of diagnosis were excluded. Patients' demographic characteristics such as age and gender, location of the primary tumor and cutaneous metastases, histopathologic properties and stage of the primary tumor, location of accompanying metastases to cutaneous metastases, and treatment methods utilized were recorded.

After the completion of primary treatment, patients were followed at three-month intervals in the first two years, at six-month intervals in two to five years, and yearly afterwards. At every visit, in addition to a detailed physical and rectal examination, serum AST, ALT, GGT, and CEA levels were studied. Colonoscopy was performed yearly whereas abdominal ultrasonography and/or computerized tomography were performed according to patient's complaints and the results of blood tests. Local recurrences, cutaneous and distant metastases detected during follow-up were recorded. Time to the appearence of cutaneous, peritoneal, and visceral metastases was calculated from the time of surgery for the primary tumor whereas time to death was calculated from both the time of surgery for the primary tumor and the time of the appearence of cutaneous metastases.

RESULTS

Demographic and clinical characteristics of the patients are shown in Table 1. The primary tumor was located in rectum in four patients, in sigmoid colon in three patients, and in ascending colon in one patient. Sigmoid resection was performed for sigmoid colon tumors whereas right hemicolectomy was done for ascending colon tumor. Anterior and abdominoperineal resections were both performed in two patients each for rectal cancer.

Histopathologic diagnosis was adenocarcinoma in all patients whereas mucinous subtype was diagnosed in five patients (62.5%). Only two patients had well-differentiated tumors whereas other tumors were either moderately or poorly differentiated. Median number of dissected lymph nodes was 19 (range 9 to 28) and the average number of positive lymph nodes was three (range one to seven). All patients were in stage III according to tumor, node, and metastases staging system and received adjuvant chemotherapy (Table 1). In addition, four patients with rectal cancer received external beam radiotherapy as a total dose of 50 Gy.

Cutaneous metastases appeared in a mean time of 25 months (range 9 to 61 months) after surgery. Cutaneous metastases were located in the anterior abdominal wall in six patients and in presacral region in two patients outside the previous incisions. Both patients with metastases in presacral region had rectal carcinoma and were previously treated with abdominoperineal resection. Cutaneous metastases presented as firm, mobile nodular lesions with irregular borders changing from pink to red in color and the number of lesions changed between three

Table 1. Demographic and clinical characteristics of the patients

	Age	Gender	Primary tumor site	PLN/DLN	CT	RT	Site of cutaneous metastases	Site of accompanying metastases	Time to Cutaneous Metastases (month)	Final status (month)
1	30	M	Sigmoid	1/25	FU+FA	–	AAW	Peritoneum	25	63, A
2	35	M	Sigmoid	2/6	FOLFOX	–	AAW	Peritoneum	12	23, D
3	43	M	Ascending	1/28	FOLFOX	–	AAW	–	37	52, D
4	50	M	Sigmoid	5/11	FOLFOX	–	AAW	Peritoneum	15	27, D
5	56	M	Rectum	2/6	FU+FA	+	PS	LR	9	16, D
6	28	M	Rectum	7/20	FU+FA	+	PS	LR	61	78, D
7	72	M	Rectum	6/19	FOLFOX	+	AAW	Liver	5	8, D
8	55	F	Rectum	1/21	FU+FA	+	AAW	Peritoneum	36	68, D

M: Male; F: Female; PLN/DLN: Positive lymph node/dissected lymph node; CT: Chemotherapy; FU+FA: 5-fluorouracil, folinic acid; FOLFOX: 5-fluorouracil, folinic acid, oxaliplatin; RT: Radiotherapy, AAW: Anterior abdominal wall; PS: Presacral; LR: Local recurrence; A: Alive; D: Dead.

and fifteen. Excisional biopsy was initially performed for one of the cutaneous metastases and histopathologic diagnosis was confirmed as adenocarcinoma in all patients. In addition to the cutaneous metastases, peritonitis carcinomatosa was detected in four patients and hepatic metastases were present in one patient on abdominopelvic computerized tomography whereas local recurrence was confirmed during colonoscopic examination in two patients. Only one patient had isolated cutaneous metastases. All patients received chemotherapy after the diagnosis of cutaneous metastases and local radiotherapy was not applied to anyone of the patients. Chemotherapy protocols used after cutaneous metastases were as follows; 5-fluorouracil, folinic acid, and oxaliplatin in four patients and 5-fluorouracil, folinic acid, and irinotecan in four patients.

During follow-up after the diagnosis of cutaneous metastases, seven patients died whereas one patient is still alive. All deaths were cancer-related due to disease progression. Mean survival time after the surgery for primary tumor and after the detection of cutaneous metastases were 42 (range 8 to 78 months) and 17 months (range 3 to 38 months), respectively. Four patients (patients 1,3,6,8) survived more than four years and one of these patients had isolated cutaneous metastases. All of the long-term survivors except one had one lymph node metastases and the ratio of positive lymph nodes to dissected lymph nodes was below 5% whereas it was over 30% for the remaining patients with shorter survival.

DISCUSSION

Previously, patients with cutaneous metastases of colorectal cancer were evaluated retrospectively when the disease was encountered in one of its rare forms. In retrospective series, patients with asymptomatic cutaneous metastases may be overlooked underestimating the real incidence rate or a poor prognosis can be assigned to the patients since the diagnosis is established in the symptomatic advanced stage. However, reporting on patients being prospectively followed as in this study helps to better define the natural course of this disease. Krathen et al.[5] reported the overall incidence of cutaneous metastases in various malignancies as 5.3% and in colorectal cancer as less than 4% in a meta-analysis of nine large scale studies assessing patients with cutaneous metastases. Tumors most commonly presenting with skin metastases are breast cancer (69%) in women and lung cancer (24%) in men.[6] Colorectal cancer takes the second place in both sexes with an incidence of 19% in men and 9% in women deserving a special attention.[6] Supporting this data, there was a male preponderance in the current study.

Cutaneous metastases can be detected at various sites on the body, however, 85% of the cutaneous metastases from gastrointestinal system malignancies occurs on the abdominal wall.[4,6,7] Although the exact mechanism of cutaneous metastases is not known, several routes of metastasis have been proposed for colorectal cancer. These are direct extension of the tumor, lymphatic spread, hematogenous spread, implantation during surgery, and spread along the embryonal remnants such as the urachus.[8,9] Most commonly, cutaneous metastases are detected on the previous incisions and at the umbilicus. Powell et al.[10] reported that 87% of the umbilical metastases originates from internal malignancies. In contrast to these findings, patients in the current study had cutaneous metastases outside the previous incisions and umbilicus which may support hematogenous spread in these cases. This may also indicate the use of a meticulous surgical technique. As expected, the site of metastases was either the anterior abdominal wall or the presacral area in all patients. Previously, the most common sites of primary tumor in the large intestine were reported as rectum (55%) and sigmoid colon (28%).[6] Similarly, 87.5% of the patients in this study had primary tumors located either in rectum or sigmoid colon.

Cutaneous metastases can occur after the diagnosis and treatment of the primary tumor (70%), concurrently with the primary tumor (10%), or as the only presenting symptom (20%) in patients with gastrointestinal malignancies.[8] Cutaneous metastases commonly occur in the first two years after the diagnosis of colorectal cancer and present as violaceous, firm, and freely mobile nodules.[8] Cutaneous lesions encountered in colorectal cancer patients similar to those described above should be approached with caution and a tissue sample should be obtained for histologic examination.

Prognosis of the patients with cutaneous metastases of colorectal cancer is poor if these patients concurrently have disseminated systemic disease. Although 41% of patients with cutaneous metastases from gastrointestinal cancers die in three months and almost all in five years, prognosis is better for colorectal cancer patients.[9,11,12] Average survival time after cutaneous metastases was reported as 18 months (range 3 to 24 months) for colorectal cancer.[11,12] Even longer survival times can be expected in patients with isolated cutaneous metastases. Patients in this study followed a similar clinical course. Those patients with cutaneous metastases occuring more than two years after the diagnosis were long-term survivors and one of the long-term survivors had cutaneous metastases as the only site of metastases. In addition, long-term survivors initially had less lymphatic tumor burden enabling them to survive longer.

Usually, better treatment results cannot be achieved in cutaneous metastases of colorectal cancer due to the accompanying systemic disease. Chemotherapy remains the only option for systemic treatment. However, brachytherapy was recently reported as an effective method of local treatment especially in patients with isolated cutaneous metastases.[13] Brachytherapy can be utilized in patients with limited number of symptomatic lesions. The total dose is 20 Gy as a single fraction.[13] Chemotherapy was the treatment of choice for patients in the current study and seems to be effective at least in a group of patients prolonging their survival more than a year after cutaneous metastases.

During the follow-up of colorectal cancer patients, the possibility of cutaneous metastases should always be kept in mind especially in patients with mucin-producing distal colorectal tumors. It is advised to excise all suspicious-looking skin lesions which will increase the number of patients diagnosed with isolated cutaneous metastases. In addition, in those patients presenting with cutaneous metastases of colorectal cancer as the first sign of disease, surgical excision and histologic examination of the skin lesions will lead to earlier diagnosis of the disease and may result in prolonged survival.

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