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BRIEF ARTICLE

Cutaneous metastases secondary to pancreatic cancer

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Abstract

AIM: To evaluate prognoses after cutaneous metastases, derived from pancreatic cancer.

METHODS: We treated two patients with cutaneous metastases from pancreatic cancer. We reviewed 40 reported patients in addition to our cases and analyzed clinical features of cutaneous metastases from pancreatic cancer.

RESULTS: The median survival time (MST) was 5 mo after diagnoses of cutaneous metastases. The cumulative 2-year survival rate was 3.5%. The most frequent site of cutaneous metastases was the umbilicus. The MST of patients who were treated with chemotherapy or chemoradiotherapy (CRT) was 6.5 mo, which was statistically longer in comparison to patients without treatment. Prognoses of cutaneous metastases are similar to other metastatic sites from pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

CONCLUSION: The prognoses of cutaneous metastases are similar to other metastatic pancreatic cancers. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

Key words: Cutaneous; Metastasis; Pancreas; Cancer; Prognosis

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INTRODUCTION

Secondary neoplasm involvement of the skin seems to be rare from an anatomical point of view. It is reported that the incidence of cutaneous metastases secondary to pancreatic cancer is 2.0% of all metastases[1] but sometimes it appears as a first symptom of advanced pancreatic cancer. Several cases of this condition have been reported, especially as umbilical metastases, that is, a Sister Mary Joseph's nodule (SMJN)[2]. The most common metastatic tumors of the skin are derived from breast, lung, stomach, colon, head and neck, renal cancers and melanoma[1,3-5]. We evaluated clinical significance of cutaneous metastases from pancreatic cancer because it has not been clearly described in detail before.

MATERIALS AND METHODS

We treated two patients and found 64 patients with cutaneous metastases from pancreatic cancer in the litera-

Table 1 Characterization of patients with cutaneous metastases from pancreatic cancer

Age (yr)	Sex	Sympton	Appearance	Skin site	Primary	Prognosis	Other metastasis	Other therapy	Author
76	F	Present	Nodule	Umbilicus	Tail	8 mo, dead	Peritoneum	Tegaful, 5-FU, OK432	Hisamoto *et al*[6]
67	F	Absent	Nodule	Abdomen	Tail	4 wk, dead	Liver	No therapy	Taniguchi *et al*[1]
69	M	Present	Nodule	Face, head	Head	5 mo, dead	Liver, lung, LN	No therapy	Taniguchi *et al*[1]
70	M	Present	Nodule	Umbilicus	Tail	8 mo, alive	Peritoneum	Tegaful, lentinan	Taniguchi *et al*[1]
67	M	Present	Inflammatory	Chest, abdomen	Not detail	5 mo, dead	Lung	No therapy	Taniguchi *et al*[1]
55	M	Present	Nodule	Multiple skin site	Tail	2 mo, dead	Lung, liver	No therapy	Ohashi *et al*[8]
53	M	Present	Nodule	Umbilicus	Tail	5 mo, dead	Peritoneum	No therapy	Miyahara *et al*[4]
76	F	Present	Nodule	Umbilicus	Tail	7 mo, dead	Peritoneum	No therapy	Miyahara *et al*[4]
72	M	Absent	Nodule	Umbilicus	Not detail	14 wk, dead	Liver, intestine	No therapy	Miyahara *et al*[4]
61	M	Present	Nodule	Umbilicus	Body	4 wk, dead	Peritoneum	No therapy	Miyahara *et al*[4]
67	M	Absent	Nodule	Umbilicus	Tail	2 mo, dead	Peritoneum	No therapy	Miyahara *et al*[4]
73	F	Absent	Nodule	Abdominal wall	Head	22 mo, dead	Abdiminal wall	No therapy	Miyahara *et al*[4]
60	M	Present	Nodule	Face, neck	Tail	2 mo, dead	Mesentery	No therapy	Miyahara *et al*[4]
62	F	Present	Inflammatory	Umbilicus	Tail	1 yr, dead	Liver, spleen	5-FU	Miyahara *et al*[4]
36	M	Present	Nodule	Umbilicus	Tail	5 mo, dead	Peritoneum	5-FU, RT	Miyahara *et al*[4]
77	M	Present	Inflammatory	Umbilicus	Tail	2 mo, dead	Lung	No therapy	Miyahara *et al*[4]
80	M	Present	Nodule	Multiple skin site	Not detail	5 mo, dead	Para-aortic LN	No therapy	Nakano *et al*[9]
78	M	Absent	Nodule	Umbilicus	Tail	4 mo, dead	Peritoneum	No therapy	Lesur *et al*[10]
65	F	Present	Nodule	Chest wall	Head	8 mo, dead	Liver	5-FU, CDDP, IOR	Horino *et al*[5]
60	F	Present	Nodule	Umbilicus	Tail	2 mo, dead	Peritoneum	Chemotherapy	Yoneda *et al*[11]
53	F	Absent	Nodule	Umbilicus	Tail	7 mo, dead	Peritoneum	Chemotherapy	Yoneda *et al*[11]
64	F	Absent	Nodule	Umbilicus	Body	8 mo, alive	Lung	Chemotherapy	Crescentini *et al*[12]
75	M	Present	Nodule	Umbilicus	Body	6 mo, dead	Liver	GEM	Okazaki *et al*[13]
82	M	Present	Nodule	Umbilicus	Head	5 mo, dead	Peritoneum	No therapy	Inadomi[14]
60	F	Present	Nodule	Umbilicus	Body	15 mo, dead	Peritoneum, ovary	GEM	Tokai *et al*[15]
73	F	Absent	Nodule	Umbilicus	Body	6 mo, dead	Peritoneum	Chemotherapy	Nagato *et al*[16]
79	F	Present	Nodule	Umbilicus	Tail	6 mo, dead	Peritoneum	No therapy	Asai *et al*[17]
65	M	Present	Nodule	Multiple skin site	Body	1 mo, dead	Liver	5-FU	Horino *et al*[18]
73	F	Absent	Nodule	Umbilicus	Tail	6 mo, alive	Supraclavicular LN	GEM	Limmathurotsakul *et al*[19]
85	M	Present	Nodule	Temple	Head	3 mo, dead	Lung	GEM	Takemura *et al*[20]
84	F	Present	Nodule	Umbilicus	Tail	4 mo, dead	Liver	No therapy	Hayami *et al*[21]
75	F	Present	Nodule	Umbilicus	Body	1 mo, dead	Liver	No therapy	Kamata *et al*[22]
50	M	Present	Nodule	Lateral abdomen	Body	2 mo, dead	Liver, brain	GEM, irinotecan	Kimura *et al*[23]
68	M	Absent	Nodule	Umbilicus	Body	4 mo, dead	Liver, LN	GEM, UFT-E, RT	Yamashita *et al*[24]
72	F	Present	Nodule	Umbilicus	Tail	32 mo, dead	Peritoneum	GEM, S-1	Hirahara *et al*[25]
67	F	Present	Nodule	Lower abdomen	Tail	3 mo, dead	Liver, LN	GEM	Pontinen *et al*[26]
70	F	Present	Nodule	Umbilicus	Tail	4 mo, dead	Liver, peritoneum	GEM	Ozaki *et al*[27]
81	M	Present	Nodule	Umbilicus	Tail	7 mo, dead	Peritoneum	S-1	Ozaki *et al*[27]
59	M	Absent	Nodule	Umbilicus	Body	11 mo, alive	Liver, peritoneum	GEM, 5-FU	Ozaki *et al*[27]
66	M	Absent	Nodule	Umbilicus	Body	18 mo, dead	Liver	GEM, 5-FU	Ozaki *et al*[27]
58	F	Present	Nodule	Lower abdomen	Body	10 mo, dead	Liver, lung, peritoneum	GEM, 5-FU	Our case
65	F	Absent	Nodule	Lower abdomen	Tail	4 mo, dead	Liver, bone, LN	GEM, RT	Our case

F: Female; M: Male; LN: Lymph node; 5-FU: 5-flurouracil; RT: Radiation therapy; CDDP: Cis-disamine dichloro platinum; IOR: Intraoperative radiation therapy; GEM: Gemcitabine.

ture searched using PubMed and Igaku Chuo Zassi (in Japanese) from 1950 to 2011. Of 66 patients, 42 were analyzed to clarify clinical features because these patients were recorded in detail (Table 1)[4-27].

We evaluated clinical parameters, including age, gender, symptoms, cutaneous metastatic site, primary site of pancreatic cancer and the receiving of chemotherapy or chemoradiotherapy (CRT). Survival curves were depicted using the Kaplan-Meier method and levels of significance were tested with the log rank test. Probability values < 0.05 were considered significant. Prognostic factors were assessed by odds ratios with 95% confidence interval using univariate and comparative analysis. Cox's proportional hazard model was used in a stepwise multivariate analysis for all parameters to identify factors independently associated with the prognosis.

RESULTS

All 42 patients were diagnosed as pancreas cancer due to histological examination from cutaneous and/or primary biopsy sample or imaging, including enhanced computed tomography or magnetic resonance imaging. The patient population comprised of 22 men and 20 women with a median age of 68 years, ranging from 36 to 85 years. Survival time ranged from 1 to 32 mo. The

Table 2 The local area of the cutaneous metastasis and the site of primary pancreatic cancer

Primary site of pancreas	Head or neck	Chest or abdominal wall[1]	Umbilicus	Multiple[1]
Head (n = 6)	2	3	1	0
Body (n = 11)	0	1	9	1
Tail (n = 22)	1	3	17	1
Unknown (n = 3)	0	0	1	2

[1]Except umbilicus.

Table 3 Univariate and multivariate analyses of prognostic factors for survival after discovery of cutaneous metastases from pancreatic cancer

Variable	Univariate analysis			Multivariate analysis		
	P-value	Odds ratio	95% CI	*P*-value	Risk ratio	95% CI
Age (≥ 68 yr/< 68 yr)	0.7552	1.4773	0.4325-5.0463	0.7527	1.2700	0.2872-5.6145
Sex (female/male)	0.0142[a]	6.3143	1.6272-24.5023	0.9090	0.9280	0.2575-3.3436
Sympton (-/+)	0.5311	1.9091	0.5082-7.1718	0.9429	1.0516	0.2657-4.1619
Skin site (umbilicus/others)	0.0982	4.2308	0.9660-18.5290	0.5571	1.8049	0.2514-12.9568
Primary site (head, body/tail)	0.6719	1.6250	0.4353-5.8240	0.9746	1.0282	0.1859-5.6854
Chemotherapy or CRT (+/-)	0.0079[a]	8.3333	1.8784-36.9695	0.8186	0.7944	0.1111-5.6778

[a]$P < 0.05$.

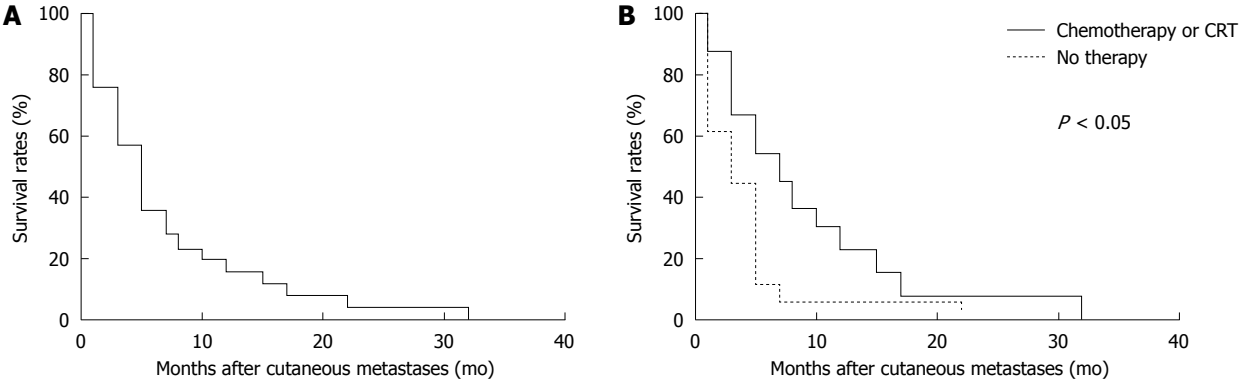

Figure 1 Kaplan-Meier survival curve. A: Survival of all patients after diagnosis of cutaneous metastasis from pancreatic cancer; B: Relationship between the presence of chemotherapy or chemoradiotherapy (CRT) and survival after diagnosis of cutaneous metastasis from pancreatic cancer.

median survival time (MST) of all patients was 5 mo after diagnosis of cutaneous metastases. The cumulative 1- and 2-year survival rate was 17.5% and 3.5%, respectively (Figure 1A).

Twenty-nine patients (69.0%) had some symptoms, including inflammatory changes such as a flare or sore in 3 patients and the painful or non-tender subcutaneous nodule in 26 patients. Cutaneous metastases were discovered by physical examination without symptoms in the remaining 13 patients (Table 1).

Sites of cutaneous metastases were head or neck in 3 patients, abdomen or chest excluding umbilicus in 7 patients, umbilicus (namely SMJN) in 28 patients and multiple sites in 4 patients. The primary pancreatic lesion was located in the head in 6 patients, body in 11 patients, tail in 22 patients and not recorded in 3 patients (Table 2). Umbilical metastases occurred in 28 patients. Primary pancreatic lesions of umbilical metastases were pancreatic body and tail in 26 patients out of 28. Incidence of umbilical metastases from cancers of pancreatic body and tail was significantly more frequent than from pancreatic head cancer (P = 0.0375).

Twenty-two patients received chemotherapy after diagnoses of cutaneous metastases. Twelve patients were treated with gemcitabine and 6 with 5-flurouracil (5-FU). Two patients received CRT. The other two patients received other chemotherapeutic agents (Table 1). There was no significant difference between treatment with Gemcitabine and 5-FU (data not shown).

Significant prognostic factors after detection of cutaneous metastases from pancreatic cancer were females and receiving of chemotherapy or CRT among six clinical variables using only univariate analysis (Table 3). The MST of the patients with chemotherapy or CRT was 6.5 mo, significantly better than 4 mo in the patients without any treatment (Figure 1B).

DISCUSSION

Pancreatic cancer is the 5th leading cause of cancer related death in both men and women in Japan[28]. The majority of pancreatic cancer is advanced at diagnosis (50.5% metastatic *vs* 8% localized, 25.9% regional spread)[29]. One of the reasons is that pancreatic cancer presents with various incomprehensive symptoms. Cutaneous metastases as the first signs of pancreatic cancer were reported in several cases[1,4,14,26,27,30]. The target of spread of pancreatic cancer substantially includes the regional lymph nodes, liver, lungs, celiac plexus, superior mesenteric vessels, ligament of Treitz, portal vein and skin[26]. The most common metastatic site of cutaneous is the umbilicus (SMJN)[4,26]. Incidence of umbilical metastases from cancers of pancreatic body and tail was significantly more frequent than from pancreatic head cancer. Our study revealed that the primary site of SMJN was pancreatic body and tail in 92.9% of patients. Yendluri demonstrated that this might relate to the propensity for tail of pancreas cancers to remain asymptomatic until an advanced stage when distant metastasis has been found[30]. Because of potential intercommunications, the umbilicus may gather a variety of tumors. The metastatic cancer cells may travel by retrograde flow from the peritoneal cavity to the umbilicus *via* the lymphatics of the falciform ligament, the median umbilical ligament of the urachus, the vitello intestinal duct remnant and the obliterated vitelline artery[30,31]. Eventually, tumor micro-embolization through the artery or the portal vein provides a channel for hematogenous implantation and seeding of umbilical tissue[2,30]. Non-umbilical cutaneous metastases are rare but distant spread shows that pancreatic carcinoma can reach all cutaneous tissues *via* blood or the lymphatic system[26]. There is no significant difference of prognosis between umbilical and non-umbilical metastases in this article (Table 3). Average survival of advanced pancreatic cancer in general is less than 4 mo[30]. Prognoses after detection of cutaneous metastases from pancreatic cancer were similar to those with metastatic pancreatic cancer.

This study demonstrated significant improvement in median overall survival from 6.5 mo *vs* 4 mo when some treatment, including chemotherapy alone and CRT, for patients with umbilical metastases from pancreatic cancer compared to no therapy. Several treatments might be performed for patients who had a good enough performance status to receive some treatment, although there is a significant difference in background between these two groups.

In conclusion, prognoses of cutaneous metastases are similar to other metastatic pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

COMMENTS

Background

Cutaneous metastases from pancreatic cancer are uncommon. Prognoses after cutaneous metastases have not been described in detail.

Research frontiers

The authors evaluated clinical significance of cutaneous metastases from pancreatic cancer because it has not been clearly described in detail before.

Innovations and breakthroughs

The median survival time (MST) was 5 mo after diagnoses of cutaneous metastases. The cumulative 2-year survival rate was 3.5%. The most frequent site of cutaneous metastases was the umbilicus. The MST of patients treated with chemotherapy or chemoradiotherapy (CRT) was 6.5 mo, which was statistically longer in comparison to patients without treatment.

Applications

Average survival of advanced pancreatic cancer in general is less than 4 mo. Prognoses after detection of cutaneous metastases from pancreatic cancer were similar to those with metastatic pancreatic cancer.

Peer review

The prognoses of cutaneous metastases are similar to other metastatic pancreatic cancer. Receiving chemotherapy or CRT was the only prognostic factor of cutaneous metastases from pancreatic cancer.

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