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Abstract

A 69-year-old Japanese woman underwent a curative operation for rectal cancer (T2, N0, M0, Dukes B, R0, and stage ⅡA of American Joint Committee on Cancer) 3 years ago. On subsequent routine follow-up, a right-side thyroid nodule and a regional lymph node of up to 1.5 cm in diameter was palpated. FDG-PET demonstrated high FDG accumulation in the right lobe of the thyroid gland, neck lymph nodes, and sacral periosteum.

We diagnosed a local recurrence of rectal cancer and a primary thyroid cancer. We chose radiotherapy for the periosteal recurrence, and then right hemithyroidectomy with regional lymph node dissection for the thyroid tumor was performed. Pathological examination demonstrated mucinous carcinoma, the same as the previous surgical specimen from the rectum. She had been treated with postoperative chemotherapy and had been alive and well for 26 months with lung metastases.

Although thyroid gland metastasis from colorectal cancer is rarely reported, physicians should consider the possibility of thyroid gland metastasis when performing routine follow-up examinations for recurrence of colorectal cancer.

Key Words: Thyroid gland metastasis; Colorectal cancer; Positron emission tomography; Vertebral venous system of metastasis

Introduction

Colorectal cancer is one of the most common malignant diseases, and some patients suffer from local recurrence or metastatic spread following curative resection of the primary site. The most frequent distant metastatic sites are liver, lung, and the lymph nodes, whereas thyroid gland metastasis from colorectal cancer is uncommon[1-4)].

Recently, we experienced a case of thyroid gland metastasis from rectal cancer, which was detected using F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) during routine follow-up.

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We herein present the case, and discuss the pathogenesis of thyroid gland metastasis from colorectal cancer with a review of the English literature.

Case Report

A 69-year-old Japanese woman had a medical history of laparoscopic low anterior resection with regional lymph node dissection for rectal cancer 3 years ago, and had undergone periodic follow-up. Before the first operation, her serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were normal. The rectal cancer consisted of moderately differentiated adenocarcinoma and mucinous carcinoma (Fig. 1), and there had been no distant metastasis or local invasion (T2, N0, M0, Dukes B, R0, and stage ⅡA of American Joint Committee on Cancer). She had not received any adjuvant chemotherapy or radiotherapy because of the curative operation.

During routine follow-up, she underwent chest and abdominal computed tomography (CT) and blood tests, and serum examination included CEA and CA19-9. Two months ago, the patient complained dyspnea, and swelling of the neck was noted. A right-side thyroid nodule and peripheral lymph nodes of up to 1.5 cm in diameter were palpated. Blood tests and serum examinations, which included thyroid hormones, CEA, and CA19-9, revealed slightly high thyroid-stimulating hormone, and microsome test and thyroid test results (Table 1), but she did

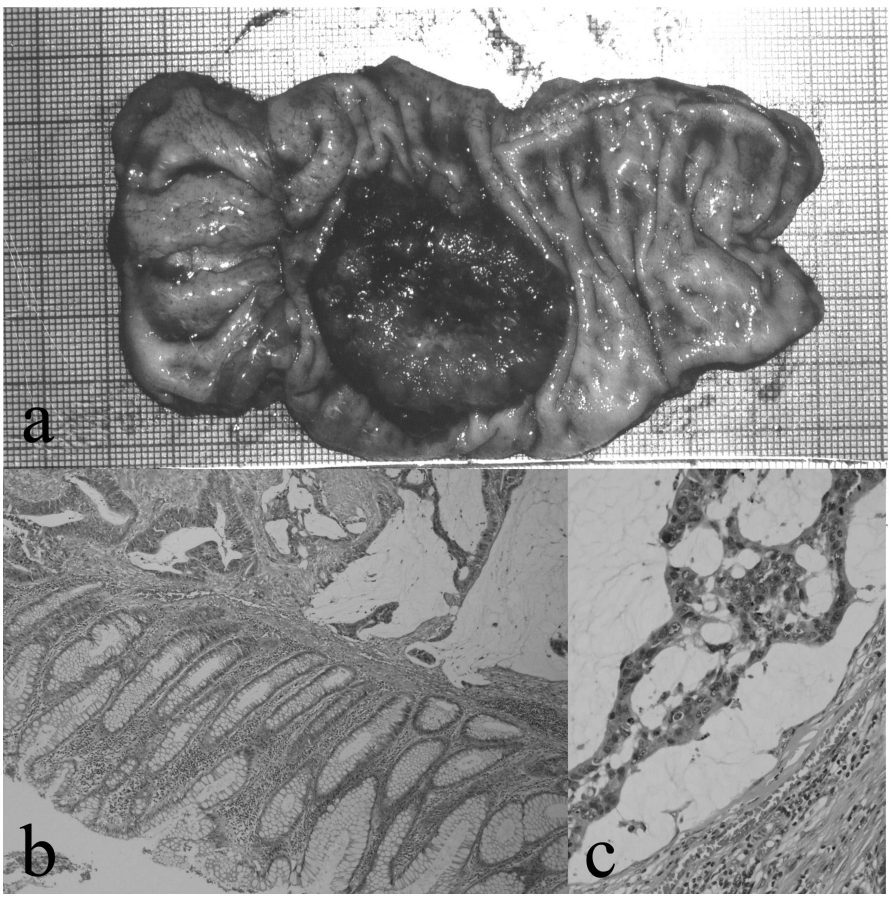

Figure 1. Macroscopic features of the surgical specimen following the first operation for rectal cancer (a). Microscopic features of the rectal cancer included moderately differentiated adenocarcinoma (b) and mucinous carcinoma (c).

Table 1. Blood tests and serum biochemical examination of the present case

White blood cells	5590	/μL	Total bilirubin	0.5	mg/dL	thyroid test	400	times
Red blood cells	423	$\times 10^4$/μL	L-asparate aminotransferase	22	U/L	microsome test	6400	times
Hemoglobin	12.7	g/dL	L-alanine aminotransferase	9	U/L	thyroglobulin	<5.0	ng/mL
Hematocrit	37.6	%	Alkaline phosphatase	443	IU/L	thyroid stimulating hormone	5.71	μIU/mL
Platelet count	24.9	$\times 10^4$/μL	Creatine kinase	79	IU/L	free triiodothyronine	3.3	pg/mL
Total protein	8.3	g/dL	Fasting blood sugar	127	mg/dL	free thyroxine	0.99	ng/dL
Na	138	mEq/L	Blood urea nitrogen	15.1	mg/dL	carcinoembryonic antigen	4.8	ng/mL
K	4.1	mEq/L	Creatinine	0.7	mg/dL	carbohydrate antigen 19-9	24	U/mL
Cl	101	mEq/L	Total cholesterol	279	mg/dL	carbohydrate antigen 15-3	23.2	U/mL
Ca	10	mg/dL	Triglycerides	92	mg/dL			

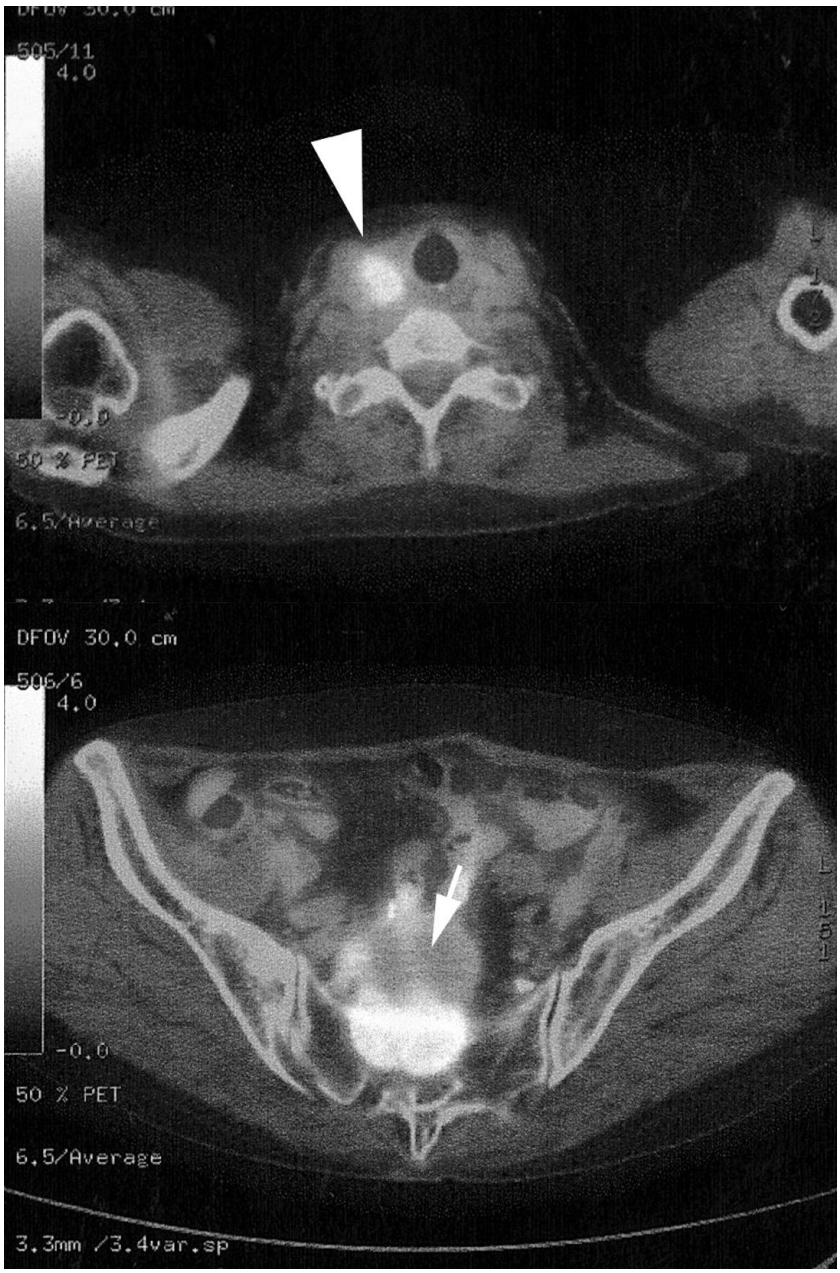

Figure 2. The F-18 fluorodeoxyglucose positron emission computed tomography demonstrated a solid lesion of the neck and thyroid gland (arrowheads), and a cystic pelvic lesion (arrows).

not show any hoarseness; dyspnea suggested local invasion of a malignant tumor. Doppler ultrasonography showed a hyperdynamic low echoic lesion of the thyroid. FDG-PET demonstrated high FDG accumulation in the right lobe of the thyroid gland, neck lymph nodes, and sacral periosteum (Fig. 2). FDG-PET computed tomography also revealed a solid lesion of her neck and thyroid gland, and a cystic pelvic lesion.

We diagnosed a primary thyroid cancer and local pelvic recurrence of rectal cancer. As the periosteal recurrence in the pelvis spread widely, we chose radiotherapy (stereotactic irradiation, totally 54 Gy, using with linear accelerator) for the periosteal recurrence, and then right hemithyroidectomy with regional lymph node dissection for the thyroid tumor was performed. Macroscopic features of the thyroid tumor included a mucinous cut surface, considered

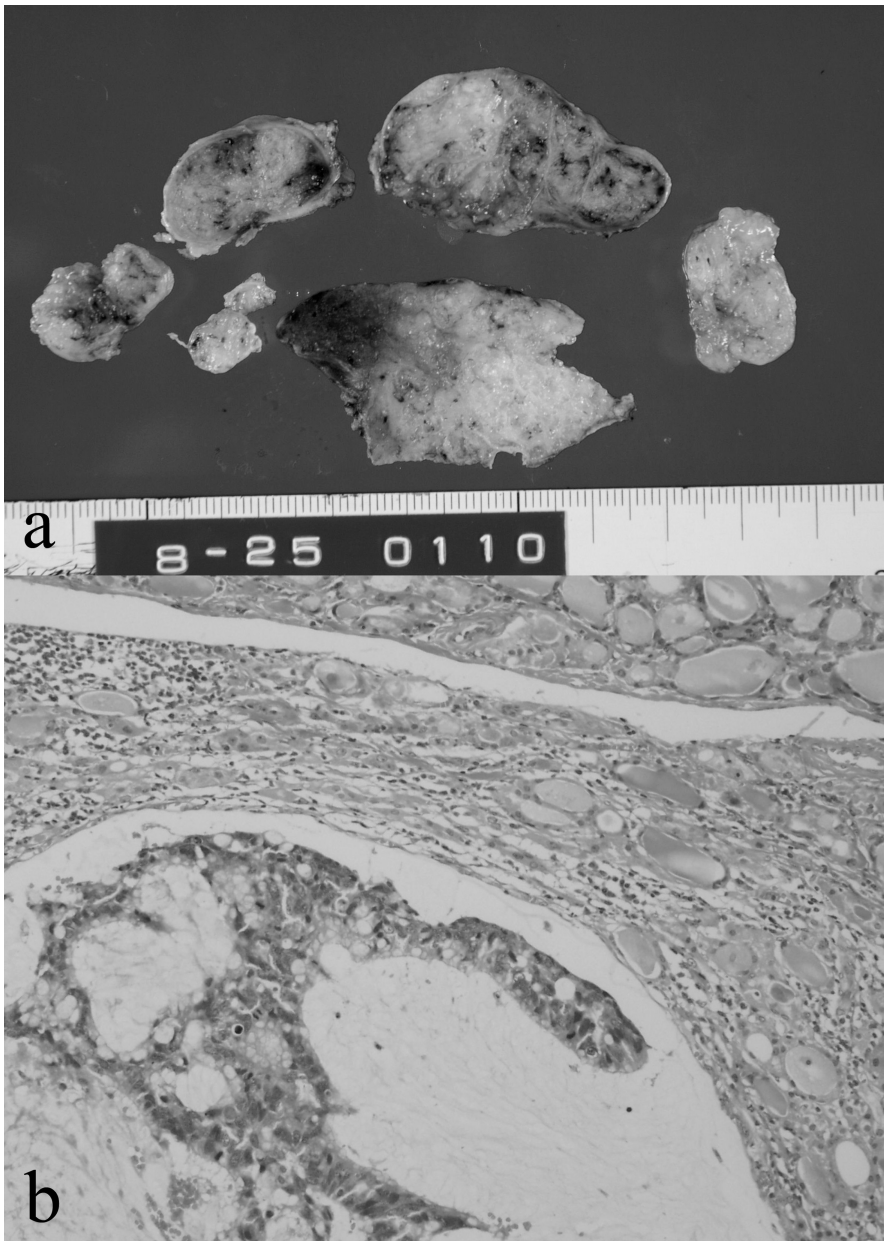

Figure 3. Macroscopic features of the surgical specimen from the second operation, for the thyroid gland metastasis (a). Microscopic features of the thyroid gland metastasis show only mucinous carcinoma identical to that of the first lesion of the rectum (b).

inconsistent with the pathologic features of primary thyroid cancer (Fig. 3). Pathologic examination of the thyroid tumor and metastatic tumor of neck lymph nodes revealed moderately differentiated adenocarcinoma and mucinous carcinoma, compared to the previous rectal cancer (Fig. 3), and we therefore made a postoperative diagnosis of recurrent rectal cancer in the pelvis and thyroid gland.

The patient's postoperative course was uneventful, and she received treatment with chemotherapy comprising modified FOLFOX6 with bevacizumab. After several cycles of FOLFOX6 with bevacizumab, severe diarrhea and bone marrow suppression occurred, and we changed the chemotherapy to bilateral internal iliac arterial injection of 5-FU via an implanted catheter. The periosteal recurrence disappeared and she is alive and well with recurrence of lung metastasis during the subsequent 26-month follow-up period.

Discussion

Colorectal cancer is one of the most common malignant diseases, and up to 40% of patients will suffer from local recurrence or metastatic spread after undergoing curative resection of the colorectal site[5]. The most frequent distant metastatic sites of colorectal cancer are liver, lung and local lymph nodes, and we usually consider these sites first when searching for distant metastases[1-4]. As thyroid gland metastasis (TM) from colorectal cancer is uncommon and very rarely seen clinically, physicians do not usually conduct examinations for TM during routine follow up.

A secondary thyroid cancer is rare, occurring at a rate of about 1%, compared with primary thyroid cancer[6-9]. Some investigators have reported that the kidney is the most common primary tumor site, followed by lung, breast, esophagus, uterus, and the skin (melanoma)[6-9]. In our research of the English literature, only 37 cases of TM from colorectal cancer have been reported[1,3-36], suggesting that TM from colorectal cancer is indeed a rare occurrence. In contrast, microscopic TM from advanced colorectal cancer has been found in 4-9% of autopsy studies[2,4].

Two hypotheses to explain the rarity of TM were proposed by Willis, and there has been considerable support for this hypothesis since this time[10]. The first, a primarily mechanical explanation, is that the extremely abundant supply of arterial blood to the thyroid, and the rapid blood flow, make adhesion and implantation of tumor cells difficult. The second hypothesis provides a more chemical explanation, that the high oxygen saturation and high iodine content of thyroid tissues inhibits the growth of tumor cells. Regarding the latter, Smith et al put forth the idea that, when an organic disorder exists in thyroid tissue, a decrease in arterial blood flow and a low-oxygen or low-iodine state result, thus increasing the susceptibility to metastasis. This is based on evidence that underlying diseases, such as adenomatous goiter, were found in more patients with tumor metastasis to the thyroid. In the present case, some abnormal ranges of thyroidal function were also documented. However, we believe that the metastasis might induce the thyroidal disorder, but the hypothesis still remains, and is really a chicken-or-egg question.

The route of metastasis to the thyroid gland is believed to be via lymphangitic as well as hematogenous pathways. The former includes direct metastasis to the thyroid gland, especially from lung and breast malignancies. The lymphangitic TM might arise secondarily to pulmonary metastases from colorectal cancer in some cases. The latter pathway might arise through portal veins, pulmonary veins, and large veins, since metastasis to the lung or liver often occurs prior to

Table 2. Clinical cases of thyroid gland metastasis from colorectal cancer

Author	Year	Sex	Age	Primary site	Stage at ocurrence	Postoperative/ Adjuvant therapy	CEA at the recurrence	Thyroid function	Timing of TM	Timing of TM	Other metastatic sites	Treatment for TM	Dead/ alive	Prognosis after TM
Willis	1931	-	-	-	-	-	-	-	-	-	-	-	-	-
Rankin	1936	-	-	-	-	-	-	-	-	-	-	-	-	-
Mayo	1941	-	-	-	-	-	-	-	-	-	-	-	-	-
Sklaroff	1954	F	73	Rectum	-	-	-	Adenomatous goiter	Meta	7y	Liver	-	Dead	-
Elliott	1960	F	-	-	-	-	-	-	-	-	-	Surg	-	-
Wychulis	1964	F	37	Rectum	Ⅲ	-	-	-	Meta	6m	-	Surg	Dead	10m
Make	1974	M	68	Sigmoid	-	-	-	-	Meta	4y	liver	RT	Dead	8m
Thomson	1975	F	44	Ascending	-	-		-	Meta	4y	thymus	Surg	Dead	1y
Lester	1986	F	55	Ascending	-	-	positive	-	Meta	9m	-	Surg	-	-
Kobayashi	1988	F	48	Rectum	-	-	6.5 μg/L	Normal	Meta	7y	lung	Surg	Alive	10m
Cristallini	1989	M	60	-	-	-	-	-	Meta	4y	none	Surg	Alive	1y
Nachtigal	1992	F	69	Sigmoid	Ⅱ	-	-	-	Meta	6y	-	Surg	Dead	8m
Shibutani	1992	F	52	Sigmoid	-	-	84.8 μg/L	High thyroglobulin	Meta	3y	lung	Surg/Chem	Dead	8m
Rosen	1995	F	46	-	-	-	-	-	Meta	-	-	-	Dead	-
Mesko	1996	F	59	Rectum	ⅡA	Chem	132 μg/L	-	Meta	2y	bone/kidney	Surg/RT/Chem	Alive	1y
Osin	1996	F	70	Rectum	Ⅳ	Chem	positive	-	Syn	0	liver	Surg/Chem	Alive	-
Takashima	1998	M	67	Rectum	-	-	-	-	Meta	2y	-	-	-	-
Kim	1999	F	68	Sigmoid	ⅡA	none	-	-	Meta	2y	neck	Surg/RT/Chem	Alive	-
Kanaya	2001	F	80	Ascending	ⅢC	none	104.5 μg/L	Low FT3/4, high TSH	Meta	1y	neck	Surg/Chem	Dead	1y3m
Shiga	2001	F	36	Rectum	-	-	-	-	Meta	3y	lung/neck	Surg/Chem	Alive	13m
Ridder	2001	F	70	Sigmoid	Ⅲ	-	21 μg/L	Hyperthyroidism	Meta	2y	-	Surg/RT	Dead	3y
Akimaru	2002	M	67	Ascending	ⅢB	-	10.9 μg/L	-	Meta	6y	lung/pleura/neck	Chem	Dead	4m
Witt	2002	M	71	Transverse	Ⅲ	-	20.3 μg/L	-	Meta	7y	liver	Surg	-	-
Fujita	2004	F	28	Rectum	Ⅳ	Chem	-	-	Syn	0	neck	Surg/Chem	Dead	6m
Poon	2004	M	64	Ascending	ⅢB/C	Chem	8.9 μg/L	-	Meta	1y	trachea/lung	Chem	Dead	1y6m
Poon	2004	F	53	Sigmoid	Ⅳ	-	-	-	Syn	0	liver/lung	Surg/Chem	Dead	10m
Seko	2004	F	48	Rectum	Ⅳ	Chem	11.1 μg/L	High thyroglobulin	Meta	2y	lung	Surg	Dead	9m
Phillips	2005	F	81	-	Ⅲ/Ⅳ	-	-	-	Meta	2y	larynx	Surg	-	-
Cavanna	2006	F	55	Sigmoid	Ⅳ	Chem / RT	-	-	Meta	2y	lung/liver/bone	Chem	Dead	2m
Hanna	2006	F	48	Descending	Ⅳ	Chem	-	-	Syn	0	lung/mediasternum	Surg/Chem	-	-
Kumamoto	2006	F	66	Ascending	Ⅰ/Ⅱ	Chem	16 μg/L	High TSH	Meta	3y	liver/lung	Surg/Chem	Alive	2m
Mattavelli	2006	F	52	Rectum	ⅢB	Chem/ RT	-	-	Meta	4y/5y	lung	Surg/Chem	Alive	2y6m
Miyazawa	2006	F	60	Rectum	-	-	246.5 μg/L	Normal	Meta	2y	lung/neck	Surg/Chem	Dead	11m
Youn	2006	M	85	Ascending	Ⅲ	Chem	1710.2 μg/L	Low FT3/4, high TSH	Meta	1y9m	lung/adrenal gland	Chem	Alive	2m
Iguchi	2007	M	51	Sigmoid	-	-	9.54 μg/L	-	Meta	2y	liver	Surg	-	-
Papi	2007	-	-	-	-	-	-	-	-	-	-	-	-	-
Papi	2007	-	-	-	-	-	-	-	-	-	-	-	-	-
Present case	2008	F	69	Rectum	ⅡA	none	4.2 μg/L	Normal FT3/4, high TSH	Meta	3y	neck/pelvis	Surg/RT/Chem	Alive	13m

Clinical reports of thyroid gland metastasis from colorectal cancer. F, female; M, male; Stage, stage of American Joint Committee on Cancer; Chem, chemotherapy; RT, radio therapy; CEA, carcinoembryonic antigenn; TM, thyroid metasatasis; Meta, metachronous; Syn, synchronous; Surg, surgical resection; y, year; m, month; and -, not documented.

metastasis to the thyroid. Sometimes there is direct metastasis to the thyroid without prior occurrence of lung or liver metastases. A possible explanation for such cases involves the potential existence of a vertebral venous system, which has long been considered possible, and this theory can explain TM from the mammary glands, kidneys, or pelvic organs[37]. There have been reports of cases, including the present case, where TM metastasis has been documented without prior pulmonary or liver metastasis. The pathogenesis could be explained by the absence of any metastasis in the liver or lung, which are the most common sites of metastasis from colorectal cancer.

Our search for English case reports revealed 38 reported cases of thyroid gland metastasis from colorectal carcinoma, including the present case; these are summarized in Table 2. The patients ranged in age from 34 to 80 years (average, 59.7 years), and 8 were male, while 23 were female, showing an overwhelming majority of women. This suggests some influence of the hormonal environment on the occurrence of metastasis. The site of origin was the rectum in the majority of cases. In most cases, high serum levels of CEA were found. The time to recurrence varied, and most cases of TM were detected following recurrence at other sites.

In the literature, the prognosis of TM from colorectal cancer is generally poor, since most patients with thyroid gland metastasis have some other advanced metastatic sites and/or local invasion to the thyroid and adjacent organs, regardless of the surgical treatment, chemotherapy, or multimodal treatments the patient may have received. Additionally, physicians often disregard the possibility of thyroid gland metastasis because of the rarity of such metastasis, and therefore TM is often only detected at an advanced stage. In patients who have undergone a colectomy, followed by the subsequent development of metastasis in the thyroid, the chances of a cure are extremely slim because multiple extrathyroidal metastases are likely to be present. TM from colorectal cancer is frequently detected after an extended period of time following the diagnosis of a complete cure of the primary tumor. This renders the diagnosis of metastasis in the thyroid more difficult.

Thyroid gland metastasis from colorectal cancer is currently considered to be a rare occurrence. However, we believe that cases of thyroid gland metastasis from colorectal cancer will increase in the future. The use of multimodal treatment for colorectal cancer can be expected to improve the overall prognosis of colorectal cancer, but this resulting increase in patient survival is likely to lead to a greater number of patients with microscopic cancer cells with the potential to develop metastases at sites once considered rare. Therefore, cancer cells might secondarily metastasize to the thyroid gland from a controlled metastatic site, e. g, lung, liver, or pelvis, due to long-term multimodal therapy. Henceforth, physician should conduct routine examinations to detect recurrence of colorectal cancer using palpatory examination, surface echography, and systemic imaging examination, e. g. PET-CT[35,36] to investigate minor recurrent sites of colorectal cancer.

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