

Critical Review

Radiation Therapy for Sister Mary Joseph's Nodule: A Review

Keisuke Sasai, MD, PhD,^{a,b,*} Masashi Kawamura, MD, PhD,^a
Kenji Okumura, MD, PhD,^c and Yasuhiro Kawai, MD, PhD^c

^aDepartment of Radiation Therapy, Misugikai Sato Hospital, Hirakata, Osaka, Japan; ^bDepartment of Radiation Oncology, Juntendo University, Graduate School of Medicine, Bunkyo, Tokyo, Japan; and ^cDepartment of Surgery, Misugikai Sato Hospital, Hirakata, Osaka, Japan

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Purpose: Umbilical metastasis, known as Sister Mary Joseph's nodule (SMJN), is a manifestation of advanced malignant disease. Patients with SMJN usually require supportive care or palliative systemic chemotherapy. However, with the increasing number of older and infirm patients, radiation therapy for SMJN is needed more frequently. Therefore, we conducted this review to provide insights into radiation treatment for this rare condition.

Methods and Materials: We searched PubMed on October 16, 2022, and obtained 275 articles that described SMJN or metastatic tumors within or near the umbilicus, as well as 255 case reports or case series (298 patients) and 20 reviews, original articles, or other study types, 1 of which also described a case.

Results: The prognosis of patients with SMJN is extremely poor. However, some patients can survive for more than 2 years. The primary organs of the umbilical metastasis are mainly in the gastrointestinal tract, including the stomach, colon, and pancreas. In addition to these organs, the ovaries, uterine corpus, and breasts are the major organs affected in women. Metastasis may be divided into 4 types according to the tumor location and mechanism of the extension: within the umbilicus, not within although existing near or adjacent to the umbilicus, in the umbilical or paraumbilical hernia sac, and iatrogenic disease. Only 7 reports described patients who received radiation therapy in detail. The patients were divided into 2 groups: a relatively long course and high total dose (approximately 45 Gy) group, and a short course and low total dose group.

Conclusions: Umbilical metastasis, known as SMJN, is a rare disease and is divided into 4 types based on the location of the disease and extent mechanism. Although the prognosis of the disease is poor, some patients survive for more than 2 years. Only 7 case reports precisely described radiation therapy. Half of the patients were treated with a short course, whereas the other half were treated with relatively high doses of up to 45 Gy.

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Introduction

Umbilical metastasis, known as Sister Mary Joseph's nodule (SMJN), is a manifestation of advanced malignant disease.¹ Although SMJNs mainly originate from intra-abdominal cancers, extra-abdominal lesions such as breast cancer also cause umbilical metastasis. Sister Mary Joseph's nodule is diagnosed by palpation and careful

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Keisuke Sasai, MD, PhD; E-mail: ksasai@juntendo.ac.jp

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observation. However, because the disease is very rare, it can be overlooked or misdiagnosed as an inflammatory change in the umbilicus in a clinical setting. Therefore, many case reports have focused on the diagnosis of the lesion to get the attention of general physicians, and treatments have been less frequently described in these papers.

A few patients, in whom the SMJN is a single metastasis, receive intensive combined therapy, including resection and systemic chemotherapy with or without radiation therapy. These patients can survive for long periods. However, an umbilical metastasis is a manifestation of an advanced malignant tumor, as previously stated, and therefore its prognosis is usually dismal. Many patients with SMJN tend to require palliative systemic chemotherapy or supportive care. The lesion can easily cause pain, tumor ulceration, oozing or discharge, and a foul smell. These symptoms deteriorate the patient's general condition and jeopardize their dignity.

We have encountered an increased number of older patients with cancer in recent years owing to advances in medicine and longer life expectancy.² According to e-Stat, a portal site for Japanese Government Statistics, 18.8 million people (15.0% of the total population) are aged 75 years or older and 6.4 million (5.1%) are aged 85 years or older in Japan.³

Older people tend to stay at home, either alone or with their aged partner or relatives, or in public facilities dedicated for older adults. Furthermore, the prevalence of dementia increases with age, and almost half of people aged 80 years or older are diagnosed with dementia.² These patients also have a higher incidence of comorbidities and are hesitant to visit a physician. Therefore, they can have more advanced diseases.

Recently, we treated a patient in her 90s with advanced SMJN from cecal cancer. She complained of severe pain, bloody and purulent discharge, and an odd odor (Fig. 1). She was referred to our hospital for radiation therapy to relieve these symptoms before being moved to a care home. Owing to the lack of sufficient studies, we

encountered the following intricate problems, which had to be solved before the commencement of treatment:

1. What dose fractionation is suitable for this patient?
2. What dose should we deliver?

Patients with painful bone metastases are usually treated with a single high dose of 8 Gy or short-course fractions such as 5 or 6 × 4 Gy. These doses effectively relieve pain in many patients with bone metastases. Clinical trials have demonstrated no significant differences in pain relief between single-dose and fractionated irradiation.⁴ However, SMJNs are soft-tissue tumors located near the digestive tract. Whether SMJN can be treated as a bone metastasis remains unclear.

The second question we asked pertained to the most suitable total dose for the lesion. Doses of up to 30 Gy are suitable in palliative settings, ranging from 8 Gy in a single fraction to 30 Gy in 10 fractions. If the effectiveness is insufficient, the lesion can be reirradiated later. However, in the case of aged patients who move back to their homes or public facilities, such as a group home or nursing home, returning for reirradiation is often impossible because of their deteriorating general condition or mental status. Therefore, we preferred to irradiate patients with the highest possible dose. Conversely, if the tumor is located within the umbilicus, there is no muscle layer or subcutaneous tissue.⁵ The tumor easily reaches the skin outward, often causing skin ulcers, and also faces the peritoneum inward. The high radiation dose may cause rapid shrinkage of the tumor, and as a result, perforation or penetration of the abdominal wall. We encountered a dilemma regarding which fractionation and total dose we should administer to this older, frail woman.

As previously stated, the number of older patients is rapidly increasing in society, and radiation oncologists frequently treat older patients. We performed a PubMed survey; however, unfortunately, we found no review articles on radiation therapy for SMJN that had been published. Therefore, we conducted this review to provide insights into radiation treatment for this rare condition.

Methods and Materials

A literature search was performed using the following inclusion criteria: original article, review, case report, or correspondence describing umbilical metastasis or SMJN written in English or Japanese. On October 16, 2022, we performed a PubMed search using the term "Sister Mary Joseph's nodule" and identified 346 studies. A further search using the term "umbilical metastasis" revealed more than 2000 papers. However, nearly all studies in this group were unrelated to metastatic tumors in the umbilicus. Articles were selected based on their titles. Finally, we added 91 possible studies to the 346 with the keyword of

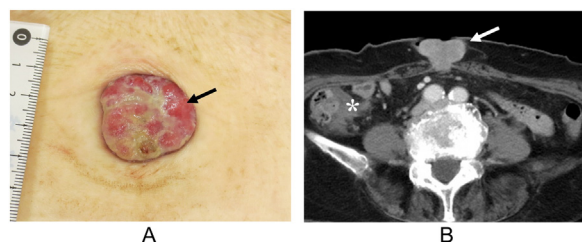


Figure 1 An older, frail woman in her 90s with Sister Mary Joseph's nodule was referred for radiation therapy. (A) The patient had a tumor (3 × 3.5 cm) (black arrow) in the umbilical region. (B) Computed tomography revealed a tumor (white arrow) extending from the skin to the peritoneum within the umbilical region and a thick cecal wall (*).

“Sister Mary Joseph nodule”, for a total of 437 papers written in English or Japanese, 319 of which were available in PDF format through the Juntendo University Medical Library. Two hundred seventy-five of the 319 papers described SMJN or metastatic tumors within or near the umbilicus; 255 were case reports or case series (298 patients) and 20 were reviews, original articles, or other study types (Appendix E1). One of the 20 articles also described a case.⁶

Results

SMJN

SMJN is relatively rare and manifests as advanced disease. The origin of metastasis varies; therefore, each case of SMJN has a wide variety of radiosensitivities. Before starting the main discussion, we will summarize this basic concept based on the literature review, which is required to perform radiation therapy.

The definition of SMJN

Umbilical metastasis, mainly from an intra-abdominal malignancy, is known as SMJN, although lesions other than intra-abdominal lesions can also cause SMJN. Sister Joseph at St. Mary Hospital, the earliest incarnation of the Mayo Clinic in Minnesota, is the eponym for this characteristic metastasis. She was the head nurse and first surgical assistant to Dr William Mayo and pointed out the clinical importance of the presence of nodules in the umbilicus on physical examination because they indicate widespread intra-abdominal metastasis of cancer.⁷ Although other investigators revealed the existence of umbilical metastasis earlier,⁸ this specific condition was named SMJN by Sir Hamilton Bailey, a British surgeon.⁹ The present definition of SMJN in *Hamilton Bailey's Demonstrations of Physical Signs in Clinical Surgery* (19th edition) is “advanced intra-abdominal malignancy (eg, adenocarcinoma of the stomach, colon, and pancreas and gynecologic cancers) may spread to the umbilicus, where such a lesion is known as SMJN.”¹

The prognosis of patients with SMJN is extremely poor. Hugen et al reported a median survival time of 7.9 months.¹⁰ Other studies have revealed an average survival time of 11 months.¹¹ However, some patients survive for more than 2 years.¹²⁻²⁴

Origin of the metastasis

In a nationwide review of pathology records in the Netherlands, Hugen et al reported that 210 men (26.1%)

Table 1 Distribution of the primary organs of SMJN based on the report by Hugen et al¹⁰

Primary site	Male, No. (%)	Female, No. (%)
Colon and rectum	101 (48.1)	101 (16.9)
Stomach	22 (10.5)	15 (2.5)
Pancreas	22 (10.5)	24 (4.0)
Cervix	-	9 (1.5)
Endometrium	-	45 (7.6)
Ovary	-	231 (38.8)
Breast	1 (0.5)	31 (5.2)
Others	25 (11.9)	36 (6.0)
Unknown	39 (18.6)	104 (17.4)
Total	210 (100)	596 (100)

Abbreviation: SMJN = Sister Mary Joseph's nodule.

and 596 women (73.9%) had umbilical metastases.¹⁰ Table 1 summarizes the primary organs of the metastases based on the report.

Umbilical metastasis mainly originates from the gastrointestinal tract, including the stomach, colon, and pancreas. No significant difference was observed in the number of patients with umbilical metastases of these origins between sexes. However, in addition to these organs, the ovaries, uterine corpus, and breasts are the major organs of origin in women. Dubreuil et al reviewed 368 cases reported in French and English between 1960 and 1995.¹¹ The primary organs were similar to those evaluated in the study by Hugen et al.¹⁰ In our review of 299 patients, there were 113 men and 184 women; 2 studies did not report the participants' sex. The most common primary organs were the pancreas (20%), colon (17%), and stomach (12%) in men. In women, in addition to these organs (pancreas [14%], stomach [10%], and colon [8%]), the ovaries (30%) and endometrium (9%) were also reported. We suppose that a strong publication bias may exist for the distribution of the original organs in this review.

Generally, more than 80% of cases were adenocarcinomas.¹⁰ Dubreuil et al reported that only 15 of 368 cases were squamous cell carcinomas.¹¹ Others, including mesotheliomas, lymphomas, and sarcomas, were histopathologically diagnosed. Because of the wide range of primary organs and the variety of histopathology, the prognosis of patients depends on these factors as well as on the extent of the disease and the patient's general condition.

Mechanisms of the development of SMJN

The mechanism of SMJN development remains unclear. Several hypotheses have been proposed, which were summarized by Balakrishnan et al as follows.²⁵

- (I) Lymphatic spread via the retrograde subserosal lymphatics from the axillary, inguinal and para-aortic nodes
- (II) Arterial spread through an anastomosis between the inferior epigastric, lateral thoracic, and internal mammary arteries
- (III) Venous spread through
 - (i) Anastomotic branches of the axillary, internal mammary and femoral veins
 - (ii) The portal system via the small umbilical veins
- (IV) Direct extension through the peritoneum
- (V) Through the urachus, the remains of the omphalomesenteric duct and falciform ligament

Among these, contiguous spread of intraperitoneal metastasis is the most common method of SMJN development.^{26,27}

Types of metastases

Diagnostic computed tomography or magnetic resonance images of the lesions were available for 139 of the 299 patients in the literature. Metastasis can be divided into 4 types according to the location of the tumor and mechanism of extension. Table 2 and Fig. 2 summarize the 4 types of SMJN.

The typical SMJN (type 1) is located within the umbilicus without any comorbidities such as surgical scars or umbilical hernias (Figs. 1B and 2A). Of the 139 lesions, 107 were this type. There is a thin layer of subcutaneous tissue and no muscle layer in the umbilicus. Therefore, these lesions easily penetrated the umbilicus from the peritoneum to the surface of the skin; 87 SMJNs were the penetrating type and 20 were the nonpenetrating type. This type of lesion, especially the penetrating type, easily causes symptoms such as skin ulcers, discharge, and a foul smell.

Some authors have reported metastatic lesions that were not located in the umbilicus but existed near or next to it (type 2) (Fig. 2B). This type of lesion usually dwells in the thick subcutaneous adipose tissue between the skin

and muscular layer; 17 patients had this type of SMJN. Ghimire et al reported a representative case (Fig. 2C).²⁸

Some patients had metastatic lesions in umbilical or paraumbilical hernias (type 3) (Fig. 2D). This type of extension appears to be a manifestation of the peritoneal dissemination of the disease. We found 5 reported cases of 139 lesions.²⁹⁻³³ Figure 2E shows a representative case reported by Rahman et al.³⁰

The last type of lesion is a lesion that is likely of iatrogenic origin (type 4). Laparoscopic or robotic surgery is now widely used to treat intraabdominal lesions, including malignant disease. The navel is a main surgical route. Therefore, the seeding of malignant cells or other mechanisms cause SMJN-like lesions in the port scar within or near the umbilicus. Traditional surgery also causes metastasis to the incisional scar, which is occasionally located near the navel. Ten of 139 reported patients showed this type of metastasis.

Radiation therapy

Thirteen studies reported that patients received radiation therapy during the treatment course.^{24,34-45} However, only 7 reported the total radiation dose administered to each patient (Table 3).

Gupta et al reported a case of gallbladder adenocarcinoma in a 32-year-old woman.³⁵ She developed an umbilical metastasis, which was treated with external-beam radiation therapy (16 Gy in 2 fractions over 2 days) and chemotherapy with fluorouracil. The lesion showed a partial response to treatment, and the patient survived for more than 8 months.

Iavazzo et al reported a case of primary peritoneal cancer, in which SMJN was the first manifestation of the disease.⁴¹ An 87-year-old woman was treated with palliative radiation therapy (16 Gy in 2 fractions) for an umbilical nodule and tamoxifen systemically. Unfortunately, the patient required wide excision of the regrowing umbilical nodule after 1.5 years, because of the malodor and increase in size.

Kumaran et al reported the case of a 52-year-old woman with SMJN from uterine cervical adenocarcinoma that had been treated 5 years earlier.⁴² She received palliative radiation therapy of 20 Gy in 5 fractions over 5 weeks, followed by systemic therapy. The umbilical nodule completely regressed.

Daniilidis et al presented the case of a 73-year-old woman with umbilical and vaginal metastases from endometrioid endometrial adenocarcinoma.⁴⁰ The patient had initially undergone surgery for the primary lesion 8 months before presentation. A second laparotomy, including full resection of the umbilical ring, omentectomy, bilateral inguinal lymph nodes, and upper one-third of the vagina, was performed. She underwent external beam radiation therapy at 20 Gy in 4 fractions over 1 week.

Table 2 Types of umbilical metastasis (Sister Mary Joseph's nodule) described in the literature

Type	Definition	No. (%)
1	Located within umbilicus	107 (77.0)
	Penetrated type	87 (62.6)
	Nonpenetrated type	20 (14.4)
2	Para-umbilical type	17 (12.2)
3	Located in umbilical or para-umbilical hernia	5 (3.6)
4	Metastasis to the port or surgical scar	10 (7.2)
Total	-	139 (100)

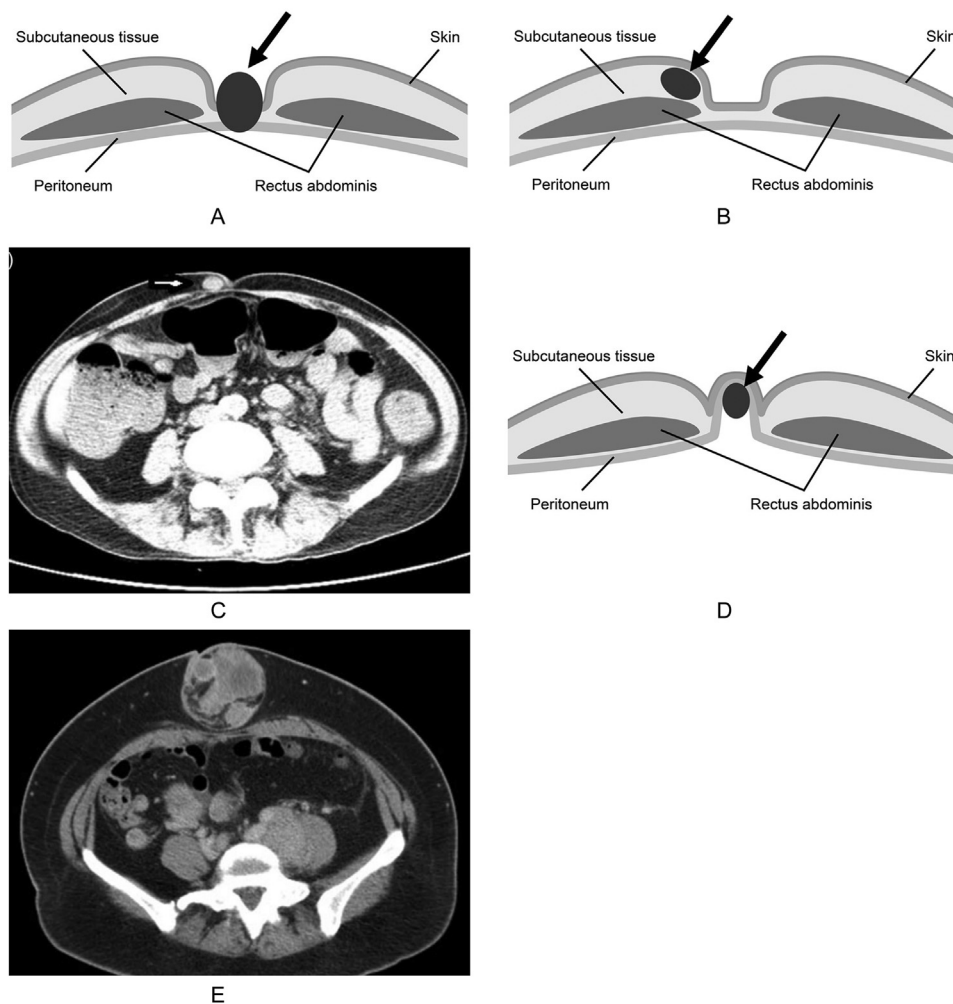


Figure 2 Schema and computed tomography image of each type of Sister Mary Joseph's nodule. (A) Type 1 tumor located within umbilicus. (B) Type 2 tumor located in the subcutaneous tissue near or next to the umbilicus. (C) A representative case of type 2 reported by Ghimire et al.²⁸ This figure was reproduced from the *Journal of Community Hospital Internal Medicine Perspectives*, 2015;5:27388. (D) Type 3 tumor located in the umbilical or paraumbilical hernia. (E) A representative case of type 3 reported by Rahman et al.³⁰ Sister Mary Joseph's nodule associated with rare endometrial squamous cell carcinoma, Rahman, M.T., Nakayama, K., Rahman, M., et al. *Arch Gynecol Obstet*, 286, 711–715, Springer, 2012, reproduced with permission from SNCSC.

Lee et al reported the case of a 75-year-old man with SMJN from gastric cancer.³⁶ The lesion shrank markedly with palliative radiation therapy (44.95 Gy in 18 fractions) and systemic chemotherapy, and the patient survived for 19 months after treatment.

Doros et al reported the case of a 14-year-old boy with umbilical metastasis from a peritoneal desmoplastic small round cell tumor.³⁸ The patient underwent resection of the intra-abdominal disseminations and systemic chemotherapy and subsequently received whole-abdomen radiation at 30 Gy with boosts for a total of 45 Gy to the right flank and umbilicus and 36 Gy to the inguinal region. No data regarding fractionation were presented. Unfortunately, the patient died of treatment-related complications after consolidation therapy with high-dose chemotherapy and autologous stem cell rescue therapy.

Hirata et al treated a 74-year-old man with SMJN from clear cell renal carcinoma.²⁴ Before radiation therapy, the patient was treated with a tyrosine-kinase inhibitor systemically and with Mohs paste locally; however, the nodule was unresponsive to these treatments. The patient was treated with external beam radiation therapy (30 Gy in 10 fractions) and high-dose-rate brachytherapy (12 Gy in 2 fractions). The tumor responded completely to treatment, and the patient survived for more than 2 years.

We treated an older woman with SMJN from cecal cancer with 45 Gy in 15 fractions over a period of 3 weeks. She had multiple metastases to the lymph nodes, lungs, liver, and bones. The umbilical tumor showed a partial response and no regrowth until her death 2 months later. During radiation therapy, she developed grade 2

Table 3 Reported cases of patients with SMJN who received radiation therapy

Authors, Y	Sex; age, y	Type of SMJN	Primary site	Pathohistology	Surgery/chemotherapy	Dose/fraction	Radiation technique	OS, mo	Dead or alive
Gupta et al, ³⁵ 2003*	Female; 32	1	Gallbladder	Adenocarcinoma	No/Yes	16 Gy/2 fr	NA	8	Alive
Lee et al, ³⁶ 2003*	Male; 75	1	Stomach	Adenocarcinoma	No/Yes	44.95 Gy/18 fr	NA	19	Dead
Doros et al, ³⁸ 2008	Male; 14	NA	Peritoneum	DSRCT	No/Yes	45 Gy/?	NA	NA	Dead
Daniilidis et al, ⁴⁰ 2012*	Female; 73	1	Uterine corpus	Endometrial carcinoma	Yes/No	20 Gy/4 fr/1 wk	NA	NA	NA
Iavazzo et al, ⁴¹ 2012	Female; 87	2	Peritoneum	Serous carcinoma	No/Yes	16 Gy/2 fr	NA	18	Alive
Kumaran et al, ⁴² 2016	Female; 52	1	Uterine cervix	Adenocarcinoma	No/Yes	20 Gy/5 fr/5 wk	NA	NA	NA
Hirata et al, ²⁴ 2022	Male; 74	1	Kidney	Clear cell renal cell carcinoma	No/Yes	30 Gy/10 fr plus ISBT, 12 Gy/2 fr	10 MVX, single AP field	24	Alive
Our case	Female; 92	1	Cecum	Adenocarcinoma	No/No	45 Gy/15 fr/3 wk	6 MVX, 2 oblique fields	2	Dead

Abbreviations: AP = anterior-posterior; DSRCT = desmoplastic small round cell tumor; ISBT = interstitial brachytherapy; MVX = megavolt x-ray; NA = not available; OS = overall survival; SMJN = Sister Mary Joseph's nodule.
 * In the cases by Gupta et al, Lee et al, and Daniilidis et al, computed tomography scans were not available; however, the lesion type was determined by photography.

(Common Terminology Criteria for Adverse Events, version 5.0)⁴⁶ anorexia and required nutritional support.

In summary, half of the patients were treated with short-course radiation, whereas others received a relatively high radiation dose and low fraction dose (2.7–3 Gy). Only 1 report described the treatment volume, the treatment technique, and the radiation dose distribution.²⁴ No reports mentioned adverse effects such as gastrointestinal events. Only our patient developed anorexia during radiation therapy.

Discussion

Only 13 case reports in which the patient received radiation therapy for SMJN were identified in this review. When SMJN is the sole metastatic lesion and the general condition of the patient is adequate, the patient may receive intensive multimodal treatment, mainly surgical resection and systemic chemotherapy. Daniilidis et al reported such a case.⁴⁰ Patients with multiple metastases and/or poor performance status tend to require supportive care or palliative systemic therapy. Although radiation therapy seems useful for this type of lesion, we revealed the rarity of its use in clinical settings. However, with an increase in the aging population, it is assumed that more patients with SMJN will require radiation therapy in the future, similar to our patient, owing to infirmity and frailty.

Sister Mary Joseph's nodules can be divided into 4 types according to location and mechanism of development. The typical form of SMJN is type 1, in which the tumor is located within the umbilicus. The direct invasion of peritoneal dissemination of the tumor to the umbilical region, which is the main mechanism of metastases and was summarized as a type IV mechanism by Balakrishnan et al,²⁵ easily causes this type of SMJN and was the focus of this review. Type 2 SMJN tumors are located not within the umbilicus but near or next to it and can be easily treated similar to other types of subcutaneous metastases. These tumors are located in the subcutaneous adipose tissue, which lies between the skin and thick muscular layers. Therefore, the possibility of abdominal wall perforation or adverse events in the gastrointestinal tract is low.

Type 3 SMJN, in which the tumor is located within the umbilical or paraumbilical hernia, does not seem to be a candidate for radiation therapy, owing to its intraperitoneal dissemination and tendency to require surgery for herniation amendment.

The treatment of the last type, iatrogenic metastasis, depends on the location of the scar. Sometimes it resembles type 1; other times, it is located outside the umbilicus, similar to type 2.

The precise dose was only reported for 7 patients who received radiation therapy. Fractionation data were unavailable for 1 patient.³⁸ Treatment intent can be divided into 2 categories; long-term control of the tumor

or palliation. Four patients, including our patient, belonged to the former group,^{24,36,38} whereas the others belonged to the latter group.^{35,40–42} Short-course radiation appears to be the mainstay treatment for SMJN because of the short life expectancy. However, 2 patients in the former group were treated successfully and survived for a long time (19 and 24 months, respectively).^{24,36} Hirata et al aggressively treated a patient with SMJN from renal cell carcinoma and achieved good results.²⁴ Radiation therapy consisted of external beam therapy of 30 Gy in 15 fractions and interstitial brachytherapy of 12 Gy in 2 fractions. This strategy of using higher radiation doses may be acceptable in some cases.

Ishibashi et al treated patients with localized pleural or peritoneal metastasis, including 2 with SMJN, and achieved good pain relief.⁴⁷ The most common radiation regimen was 30 Gy in 10 fractions; however, some patients received total radiation therapy doses ranging from 45 Gy in 25 fractions to 56 Gy in 28 fractions. The overall response to pain relief was reported in 9 of 16 patients with pain before radiation therapy.

Unfortunately, owing to the lack of sufficient experience in irradiating SMJN, establishing definitive criteria for candidates with a relatively long course of treatment is difficult. Iavazzo et al reported a patient with primary peritoneal cancer treated with 16 Gy in 2 fractions and tamoxifen who survived longer than 18 months and ultimately required surgical resection of the umbilical tumor.⁴¹ A higher radiation dose may be appropriate in such cases.

To our knowledge, no adverse events during radiation treatment or abdominal wall perforations due to rapid tumor shrinkage have been reported in previous studies. Only our patient complained of anorexia during the course of radiation. The SMJN is located in the umbilical area and is usually a relatively small lesion; therefore, the volume of normal tissue, such as that of the digestive tract, included in the radiation field is very limited. Probably many other factors not directly related to the radiation therapy, such as anxiety, a muggy climate during the radiation treatment course, or the frailty of the patient owing to old age, could have led to the symptom.

Limitations

SMJN is a very rare medical condition; therefore, the number of published studies is insufficient, especially studies on its treatment. This review aimed to provide definitive information on radiation therapy for this specific condition. However, owing to the lack of sufficient data, we were only able to include 8 case reports of patients who received radiation therapy, 7 from the literature and 1 from our own experience. Patients were treated with a wide range of doses and fractions. However, we believe that this information will assist radiation oncologists with treatment planning for this rare metastasis.

Conclusion

Umbilical metastasis, known as SMJN, is a rare disease and is divided into 4 types based on the location of the disease and extent mechanism. Although the prognosis of the disease is poor, some patients survive for more than 2 years. Only 7 case reports precisely described radiation therapy. Half of the patients were treated with a short course; half were treated with relatively high doses of up to 45 Gy.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101321.

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