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**Skeletal muscle metastasis from colorectal adenocarcinoma: A literature review**

Kulkarni N *et al.* SMM from colorectal adenocarcinoma

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## **Abstract**

### **BACKGROUND**

Colorectal adenocarcinoma is the third most common cancer worldwide. It accounts for almost 10% of all cancer-related deaths. Skeletal muscle is a very unusual site for metastasis from colorectal cancers and is associated with a poor prognosis and high mortality.

### **AIM**

To review the literature for cases of skeletal muscle metastasis (SMM) from colorectal adenocarcinoma.

### **METHODS**

A systematic literature search using a validated search strategy was carried out to identify the incidence of SMM associated with colorectal adenocarcinoma. The studies identified were tabulated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, and data was extracted in a tabulated form.

### **RESULTS**

Twenty-nine studies were included in this literature review. SMM was most commonly detected in the thigh muscles. Most of the tumours had originated from the rectum or the right colon. The histopathology of the primary tumour was generally advanced. The mean time interval between the primary tumour and onset of SMM was 22 mo. In 3 cases, asymptomatic SMM had been picked up by advanced imaging systems, like fluorodeoxyglucose-positron emission tomography scan.

### **CONCLUSION**

SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early use of advanced imaging

techniques and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

**Key Words:** Skeletal muscle; Metastasis; Colorectal cancer; Adenocarcinoma; Systematic review

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**Core Tip:** Skeletal muscle metastasis (SMM) from a colorectal adenocarcinoma is a rare complication. Presentation usually occurs at a late stage, and prognosis remains poor. However, with a high index of suspicion and early use of advanced investigative modalities, like fluorodeoxyglucose-positron emission tomography scan, SMM can be detected and treated at an earlier stage. Further research is required to better understand the prognosis and pathophysiology of SMM.

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## **INTRODUCTION**

Colorectal cancer is the third most common cancer worldwide, with at least 1.8 million new cases reported across the globe in 2018, and accounting for almost 10% of all cancer-related deaths worldwide<sup>[1,2]</sup>. Fortunately, there have been significant improvements in the life expectancy and survival rates after colorectal cancer. In particular, over the last 40 years, 5-year survival rates after a diagnosis of colorectal cancer have increased from 22% to 57%<sup>[2]</sup>. The improvement in survival has been attributed to a plethora of reasons, including screening and surveillance programmes, advanced endoscopic diagnostic and therapeutic techniques, use of minimally invasive surgical approaches (like laparoscopic and robotic techniques), and refined adjuvant and neoadjuvant chemotherapy and radiotherapy options.

Metastasis of colorectal cancer occurs *via* lymphatic, hematogenous and direct-spread routes, with the most common secondary sites being the liver, lungs,

peritoneum, lymph nodes, and bones<sup>[3]</sup>. Intriguingly, although skeletal muscles constitute almost 50% of the total body mass, the incidence of metastasis to skeletal muscles from all forms of cancers is extremely low<sup>[4]</sup>. Many studies have commented on the possible reasons for the relatively low incidence of metastases to skeletal muscles. Hypotheses include variable blood flow to skeletal muscles, rare incidence of microvasculature damage due to cancer cells in skeletal muscles, and production of a low molecular weight non-protein factor that may inhibit tumour cell proliferation<sup>[5]</sup>.

The aim of this study was to review the literature for cases of skeletal muscle metastasis (SMM) from colorectal adenocarcinoma.

## **MATERIALS AND METHODS**

A systematic literature search was carried out in December of 2021, using a validated search strategy as described below.

### ***Search strategy***

The search was performed using the PubMed, Medline, Embase, Cochrane Library and Google Scholar databases. Journals, as well as society websites, were also searched using the search terms “skeletal muscle metastasis”, “colorectal cancer”, “case reports”, and “review.” The search strategy was standardized using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two researchers (Khalil A, Bodapati S) reviewed the summary and abstracts of the articles. A full-text review was then performed by all three authors.

### ***Inclusion criteria***

Articles that were not available in English language were excluded from the study. Only studies with full texts available that included data for pathological evidence of SMM from colorectal origin were considered. Studies with pathology data other than adenocarcinoma were excluded. No other exclusion criteria were used. The data were extracted by the three researchers and included patient characteristics, year of

publication, site of primary tumour, presenting symptom, type of surgery performed for the primary lesion, site of skeletal and non-skeletal metastasis, time interval for onset of skeletal metastasis, and final outcome.

Information about the number of relevant citations, number and reasons of studies excluded after full assessment, as well as number of studies included in the systematic review fit in a well-designed PRISMA diagram, as presented in Figure 1.

## **RESULTS**

### ***Characteristics of studies***

The initial search yielded 138 eligible studies, of which 29 ultimately fit our inclusion criteria for the review (all case reports). These studies covered a total of 30 patients. Detailed characteristics of the studies are shown in Table 1.

### ***Patient profiles***

<sup>2</sup> The median age of the patients was 67 years (range: 23-83 years), with 19 male patients and 11 female patients. The primary tumour was present in the right colon in 10 patients, transverse colon in 4, left colon in 5, and rectum in 11. The presenting symptoms were pain (6 patients), palpable lump (4 patients), painful lump (9 patients), and ocular symptoms (2 patients). Three of the patients had the SMM incidentally diagnosed by imaging. Only 3 of the reported cases mention an early primary lesion (tubulovillous adenoma with high-grade dysplasia or T2 stage tumours). Six cases reported indicated that the primary lesion was of an advanced nature (T3 or T4). The tumours were either moderately or poorly differentiated in 6 cases. Four of the reported cases indicated that the primary lesion was either a mucin-secreting tumour or signet ring cell tumour.

### ***SMM distribution***

The mean time interval between the diagnosis of the primary tumour and presentation of SMM was 22 mo. Six cases were diagnosed synchronously with the metastasis. There

were a wide range of skeletal muscles that were involved in the metastasis, as follows: upper limb (extensor carpi ulnaris, thenar, deltoid, biceps); lower limb (thigh, tibialis anterior, semimembranous, adductor, sartorius, vastus lateralis); trunk (teres major, glutei, external oblique, neck muscles, paraspinal, rectus abdominus, intercostal, psoas, piriformis); and, extraocular muscles (lateral rectus, superior rectus). However, the most common site of metastasis was the thigh muscle. In 8 cases, the skeletal muscles were the only site of metastasis.

There was no detailed information about the duration of follow-up and final outcome of the disease; however, 10 case reports mentioned that the patients did not survive the disease.

## **DISCUSSION**

Colorectal cancers account for 10.7% of all new cancers reported worldwide<sup>[2]</sup>. Our literature review has shown that since 1970, only 30 cases of SMM due to colorectal adenocarcinomas have been reported. This highlights the extremely low incidence of skeletal muscle as a metastatic site due to colorectal adenocarcinoma.

The primary pathology in the majority of the patients was in the rectum (11 patients) and the right colon (10 patients). Left-sided colonic tumours accounted for 5 of the cases and transverse colon for 4. A large meta-analysis carried out by Prasanna *et al*<sup>[6]</sup> highlighted the different metastatic patterns of colorectal cancers, depending on the site of the primary tumour. This study showed that right colonic tumours were more frequently associated with peritoneal seeding, and rectal tumours were more frequently associated with lung, brain and bone metastases compared to left colonic tumours. Though SMMs were not mentioned in this meta-analysis, the general pattern of higher metastases in right colonic and rectal tumours was also seen in our review. Only 8 patients had no documented simultaneous metastasis in non-skeletal muscles. The other patients had metastases in non-skeletal muscle sites.

The most common presenting symptom of the SMM was a painful lump (9 patients). Six patients had a palpable lump with no description of pain, and 6 patients

had pain as the presenting symptom. Three patients had the SMM diagnosed incidentally by imaging. The importance of advanced imaging techniques, especially fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, for diagnosis of SMM has been highlighted by Emmering *et al*<sup>[7]</sup>. Lesions that cannot be detected by routine contrast computed tomography or magnetic resonance imaging can be observed by FDG-PET scans. FDG-PET had a significant impact on early diagnosis and patient management in 51% of cases with muscle metastasis. Hence, if there is a suspicion of SMM, the early use of FDG-PET should be encouraged for diagnosis.

Our review showed that most of the primary tumours were of an advanced nature (either T3 or T4 with positive lymph node status and poor differentiation). Three patients had mucinous features, and 1 patient had signet ring cell features. This raises the possibility that colorectal cancers with advanced aggressive features on the primary pathology have a higher incidence of SMM. Studies have shown that colorectal cancers with advanced pathological features have worse outcomes than early cancers<sup>[8]</sup>. It has been proposed that the presence of other coexisting pathologies could increase the chances of getting SMM due to colorectal adenocarcinomas. Landriscina *et al*<sup>[9]</sup> commented that dermatomyositis and other paraneoplastic syndromes could increase the chances of getting SMM. Kanani *et al*<sup>[10]</sup> also documented a case of multiple SMM associated with colorectal adenocarcinoma and non-Hodgkin's lymphoma with ulcerative colitis. However, no other studies in our literature review commented on any other coexisting pathologies.

The use of minimally invasive approaches has revolutionized the surgical treatment of colorectal cancers. Colorectal resections are now routinely undertaken with the laparoscopic and robotic approaches. Patients have smaller incisions, shorter hospital stays and equal oncological outcomes<sup>[11]</sup>. The use of laparoscopic surgery for colorectal procedures started in 1990 but became more widespread only in the 21<sup>st</sup> century. Our case reports were from a lengthy time period, beginning in 1970. Only two case reports specifically mention the use of a laparoscopic approach for the resection. Previous studies have shown that the incidence of distant metastasis and peritoneal



seeding is not different between laparoscopic and open approaches<sup>[12]</sup>. In our search, we did not find any studies that observed that the laparoscopic approach led to fewer distant metastases. However, due to the advantage of decreased environmental exposure due to operating in closed cavities and smaller incisions, the possibility always remains that peritoneal seeding and subsequent metastasis incidence could be lower in minimally invasive approaches.

The incidence of SMM was detected in up to 5.6% of patients in a post-mortem series of cancer patients<sup>[13]</sup>. However, the incidence of SMM due to colorectal cancers is still extremely low and has been reported to be about 0.028%<sup>[14]</sup>. The outcome from SMM is generally poor. A large study investigating soft tissue metastases postulated that the survival time from diagnosis to death is 5.4 mo<sup>[15]</sup>. The studies included in our review were all case reports, and the duration of follow-up was not documented in most of these studies. Hence, it is not possible to comment on the exact mortality of SMM from our study. However, the presence of SMM generally indicates disseminated disease, which would indicate a very poor prognosis.

There have been previous studies that have studied the incidence of SMM due to colorectal cancer<sup>[16]</sup>. However, we found SMM has been documented in 30 patients in the literature. We believe that this is the maximum number of cases of SMM due to colorectal cancers that have been reported in the literature. All the studies identified were case reports, and very few of these had long-term follow-up. Hence, it is not possible to definitely comment on the treatment strategies and long-term outcomes for these patients. This study again highlights that there is a paucity of literature on SMM due to colorectal adenocarcinoma. This is certainly a field that needs more research in the future.

## **CONCLUSION**

Our review showed that SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early

use of advanced imaging techniques like FDG-PET and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Skeletal muscle metastasis (SMM) is a rare complication of colorectal adenocarcinomas. The study was conducted to explore, in more detail, the present literature of this unusual finding.

### ***Research motivation***

The study encompassed a thorough review of the present literature on SMM due to colorectal adenocarcinoma. Our goal was to highlight the significance of this type of metastasis and increase awareness for early diagnosis and detection.

### ***Research objectives***

The aim of this study was to review the literature for cases of SMM from colorectal adenocarcinoma.

### ***Research methods***

A systematic literature search was carried out in December 2021. The search strategy was standardized using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### ***Research results***

SMM were most commonly detected in the thigh muscles. Most of the tumours originated from the rectum or the right colon. The mean time interval between the primary lesion and onset of SMM was 22 mo.

### ***Research conclusions***

Our review showed that SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early use of advanced imaging techniques, like fluorodeoxyglucose-positron emission tomography, and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

### *Research perspectives*

This study again highlights that there is a paucity of literature on SMM after colorectal adenocarcinoma. This is certainly a field that needs more research in the future.

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