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INVITED REVIEW

Small Bowel Adenocarcinoma in the Setting of Crohn's Disease: A Systematic Review of the Literature

Crohn Hastalığıyla İlişkili İnce Bağırsak Adenokarsinomu: Sistematik Derleme

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ABSTRACT

This study aimed to conduct a systematic literature review of small bowel adenocarcinoma (SBA) associated with small bowel Crohn's disease (CD). A systematic literature review was conducted using MEDLINE, PubMed, Embase, CINAHL, Cochrane and Google Scholar databases. Data regarding demographics, presentation, diagnosis, treatment and survival were extracted. The review included articles that reported the location of SBA in the setting of CD and excluded articles that did not state the CD location and/or cancer type. We identified 218 patients diagnosed with SBA in the setting of small bowel Crohn's disease. SBA should be in the differential diagnosis in patients with long-standing ileal CD presenting with small bowel obstruction, anaemia and perforation. SBA in the setting of CD presents diagnostic and treatment challenges; however, a high clinical index of suspicion may lead to early diagnosis and increased survival.

Keywords: Adenocarcinoma of the small bowel, Crohn's disease, small bowel cancer

ÖZ

Bu çalışmanın amacı ince bağırsak Crohn hastalığıyla (CH) ilişkili ince bağırsak adenokanseri (İBA) hakkında sistematik literatür derlemesi yapmaktır. MEDLINE, Pubmed, Embase, CINAHL, Cochrane and Google Scholar portalları kullanılarak sistematik bir derleme yapılmıştır. Hastaların demografik bilgileri, prezentasyon, tanı ve tedavi süreci ve sağkalım bilgileri analiz edilmiştir. Bu derlemeye sadece ince bağırsak CH kapsayan çalışmalar dahil edilmiş, CH'nin lokalizayonu veya kanser turunun açıkça belirtilmediği çalışmalar derlemeye dahil edilmemiştir. Toplamda ince bağırsak CH ile ilişkili olarak ince bağırsak adenokanseri tanısı alan 218 hasta saptanmıştır. İnce bağırsak adenokarsinomu, uzun sureli ileal CH olan ve ince bağırsak obstruksiyonu, perforasyonu veya anemisi olan hastaların ayırıcı tanısında akılda tutulmalıdır. CH ile ilişkili İBA'sı tanısı ve tedavisi zor bir hastalıktır, ancak yüksek bir şüphe indeksi erken tanı almayı sağlayarak sağkalımı uzatabilir.

Anahtar Kelimeler: İnce bağırsak adenokarsinomu, Crohn hastalığı, ince bağırsak kanseri

Introduction

Small bowel cancer (SBC) is a rare entity that can be associated with Crohn's disease (CD).[1] The incidence of SBC in patients with CD is increased 18.75-fold than in the normal population.[1] The pathogenesis of SBC in the setting of CD is not fully understood, but the disease has a poor prognosis due to diagnostic challenges and concluding late stage presentation associated with the primary disease. This study aimed to conduct a systematic literature review of small bowel adenocarcinoma (SBA) associated with small bowel CD (SBCD).

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Materials and Methods

Data Search

A systematic search on published literature was conducted using the PRISMA guidelines.[2] The literature search was performed on MEDLINE, PubMed, Embase, CINHAL, Cochrane and Google Scholar, and the databases were searched systematically by screening all publications between January 1947 and January 2017. In addition, Google search engine was used. Citations from the included articles were also searched, but they revealed no other relevant articles. The final query date was 2 January 2017. Information regarding keywords and medical subject headings is summarised in the PRISMA flow (Figure 1). The limitations during search were "species human" and "age ≥18."

Inclusion/Exclusion Criteria

Case reports, case series, comparative studies, clinical trials, controlled clinical trial, randomised controlled trial and cohort studies were included for PubMed and articles for Embase. Two cases of SBA associated with SBCD from our institution were included as well. Systematic reviews and meta-analyses were excluded. Articles were selected for full text reading if the abstract reported on malignancy in CD. Full text of the relevant studies were retrieved for further selection. Studies containing mixed series of colonic and SBCD were included if data on patients with SBCD diagnosed with SBA could be isolated and extracted. Studies that did not clearly report the location of CD or studies including only colonic CD, ulcerative colitis, familial adenomatous polyposis and other polyposis syndromes were excluded.

Data Collection and Analyses

The authors reviewed the full text articles that met the inclusion criteria and extracted information on study population characteristics: age at CD and SBA diagnosis, gender, initial/presenting symptoms and CD and SBA location, diagnosis timing (preoperative, intraoperative

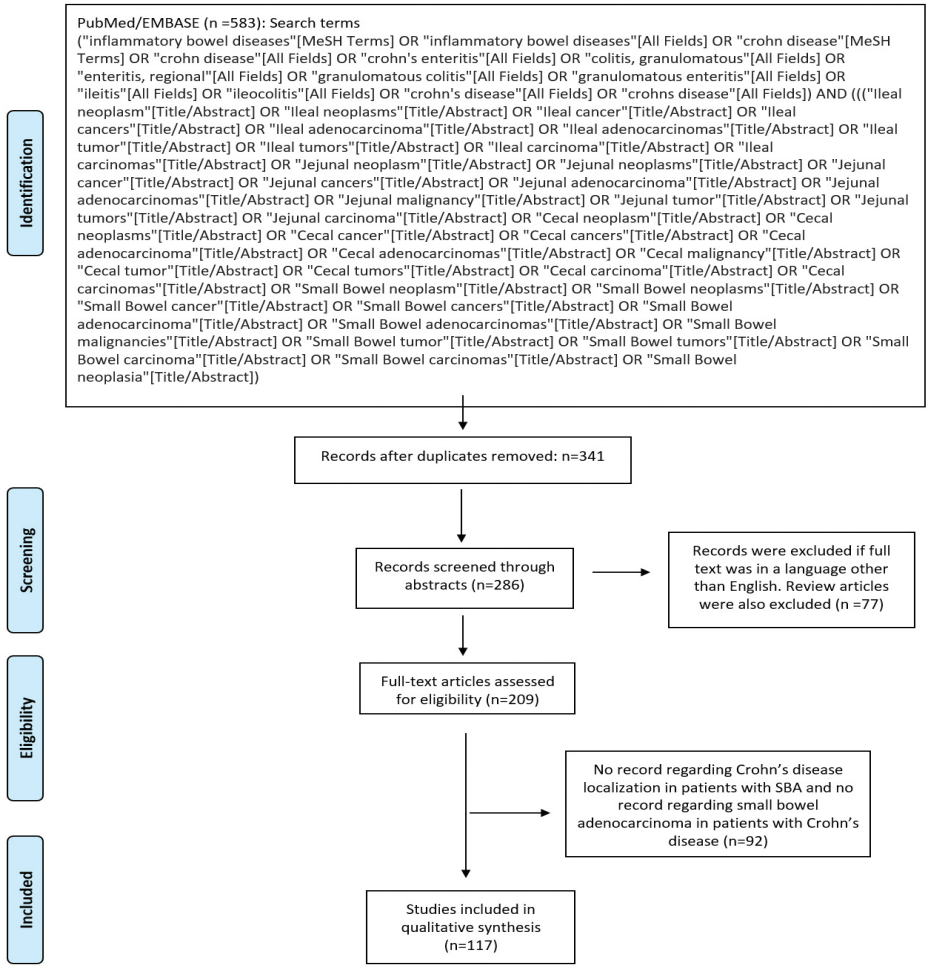

Figure 1. Flow diagram

and postoperative), tumour location, time from initial diagnosis (CD) to SBA diagnosis, stage/cancer spread[3] and survival outcomes. The CD location was reported per Vienna classification (Figure 2).[4] The diagnosis timing of the SBA was grouped into three: preoperatively if the primary tumour and/or the metastasis were diagnosed or suspected for malignancy with preoperative diagnostic studies, intraoperative if the diagnosis of the tumour was made either under direct vision or with frozen pathology report during surgery, and postoperative if the diagnosis was established with postoperative final pathology report. We identified 218 patients from 117 studies (2 patients from our institution; unpublished data).[5-121]

Epidemiology

More than half of the patients with CD experienced SB involvement during their lives.[88,122] There is a link between CD and SBA; however, the pathogenesis has not been delineated because of the rarity of the disease. One proposed hypothesis is that chronic inflammation of CD might be the accelerating factor in cancer development, but this theory has not been substantiated. The lifetime prevalence of SBA in patients with SBCD is 0.3-3%, and the risk of SBA is 18.75 times greater in patients with SBCD than in the general population.[1,21,55,77,119] A single-centre study identified only one SBA in 295 CD patients (0.3%) during a 30-year period.[21] CD associated with SBA is reported to be more frequent among men with a male-to-female ratio of 3:1; however, there is no gender-related difference in the prevalence of non-CD associated with SBA.[48,123]

We identified 218 patients from the literature, including two unpublished cases from our institution, who were diagnosed with SBA in the setting of SBCD. The detailed information regarding our cohort is summarised in Table 1.

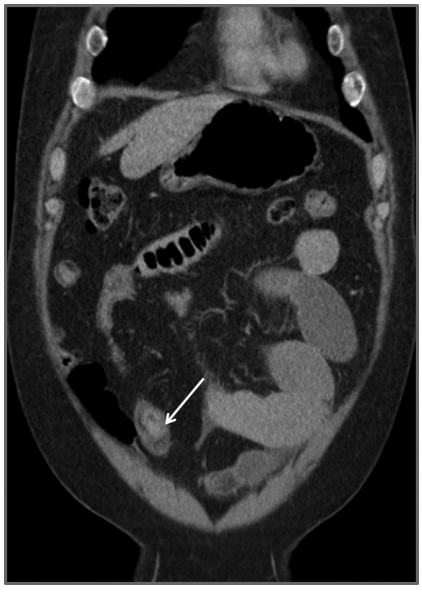

Figure 2. Computed tomography enterography from 2015 reveals changes of Crohn's disease affecting the mid to distal ileum (arrow)

In a comparative study, patients diagnosed with SBA in the setting of SBCD were younger than those diagnosed with sporadic SBA [43 (33-72) vs 48 (41-95) years old].[80] Although there are no recommendations for screening SBA in patients with CD, keeping the diagnosis germane to the clinician might impact diagnosis timing. In our cohort, the mean age of SBA diagnosis was 50.6 (range 24-86) years. The male predominance was consistent with the literature.

Risk Factors

Multiple risk factors have been proposed to play a role in the development of SBA in patients with CD.[124] Adenocarcinoma development in the setting of previous strictureplasty site has been reported in four cases,[75,78,82,109] and adenocarcinoma development in the stricture site has been reported in eight cases.[46,68,69,70,73,81,87,89] Partridge and Hodin[78] described malignant transformation in patients with a history of strictureplasty as being a (1) development of a new cancer in the area of previous strictureplasty and (2) failure to recognise the cancer due to the limited intervention without SB resection. The absence of a well-defined mass in most of the cases might preclude the diagnosis (Figure 3); thus, biopsy of the strictures adjacent to mucosal ulcers might be useful if there is a clinical concern, especially in long-standing disease.[78] A case report revealed a 49-year-old man with long-standing CD who underwent surgery due to SB obstruction and was subsequently diagnosed with multiple SB strictures in an ulcer adjacent to a stricture on intraoperative biopsy. An inconclusive frozen pathology report led to the decision to perform SB resection (Figure 4). SBA was identified in the final pathological specimen.[78] Marchetti et al.[68] reported another case where a biopsy of a stricture secondary to ileal CD was performed before Heineke-Mikulicz strictureplasties. Biopsies were negative

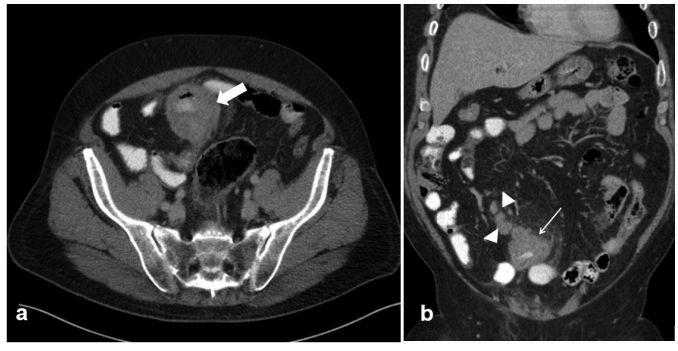

Figure 3. a) Axial computed tomography (CT) image obtained 15 months later shows bulky mass with soft tissue attenuating wall (arrow) representing the adenocarcinoma. b) CT from the same patient/time reveals that a soft tissue mass has grown within the previously affected bowel loop (arrow) with associated infiltrative changes in the local small bowel mesentery. Multiple lymph nodes have also appeared (arrowheads)

at the time of surgery, but 6 years after the surgery, the patient was diagnosed with adenocarcinoma at the site of prior strictureplasty, which was identified by a previously placed clip. In spite of these two case reports, the overall risk of SBA in the strictureplasty site is so low that routine biopsy of all strictures is not warranted.[68]

The presence of an intra-abdominal fistula is another pathologic state that has been proposed to be associated with SBA development in patients with CD.[71,96] However, it is unclear whether the SBA originates at the fistula site or fistulas occur secondary to SBA. Irrespective of the above theories, the incidence of SBA in the setting of intra-abdominal fistula associated with CD is extremely rare. A previous history of bypassed bowel segments is also a risk factor and has been reported in numerous cases.[5,10,11,12,13,14,15,16,17,18,19,20,22,24,38,40,41,49,65]Bacterial inoculation

Table 1. Information regarding 216 patients-cohort collected with literature review

Age at the diagnosis of CD, years*,1	34.4 (6-78) age <40 years old: 134 patients, age ≥40 years old: 77 patients
Gender[1]	78 female, 127 male
Age at the diagnosis of SBA*,1	50.6 years (range 24-86)
Disease duration, months[1]	20.7 (range 1-300) 27 patients diagnosed with cancer during their initial visit and they didn't included in the calculation of disease duration
Location of the CD, n L1: Terminal ileum L2: Colon L3: Ileocolic L4: Upper gastrointestinal tract	L1: 117 L1-L4: 18 L2-L4: 2 L3: 36 L3-4: 6 L4: 13 Diffuse small bowel CD or enteritis: 24
Bypassed bowel segment	24 patient have history of bypass and 22 of these patients had the SBA in the bypassed segments
Intraabdominal fistula	4 patients had the SBA in the fistula site
Stricture/stricturoplasty	12 patients have history of SB stricture, 8 patients developed cancer in the stricture site, 4 developed cancer in the stricturoplasty site
Location of the cancer	-206 patients with one adenocarcinoma: Ileum- 154, Jejunum- 28, SB- 18 (no details) Jejunoileal- 4, Ileocolic- 2 -10 patients with more than one adenocarcinoma: Ileum-colon- 7, Duodenum- ileum- 1, Jejunum-ileum- 1, Jejunum-ileum-colon-1 In addition to adenocarcinoma 4 patients were diagnosed with colorectal carcinoid tumors at the diagnosis.
Presenting symptoms	82 obstruction, 12 pain, 11 anemia/bleeding, 10 diarrhea, 8 perforation/peritonitis, 5 fistula, 3 flare, 2 ileus, 2 mass, 2 fatigue, 1 high stoma output.
Survival§,1	In 132 patients followed with a mean follow up time of 19 mo (0.1-156 mo), 4 patients were reported to die within a year of surgery- no details. 68/128 patients (53.1%) were alive at 1 year, 36/118 patients (30.5%) were alive at 2 year.
Chemotherapy (CT)	A total of 37 patients had information; 27/75 patients (36%) in stage 4, 4/33 patients (12.1%) in stage 3, 4/46 patients (8.7%) with stage 2 and 1/16 patients (6.3%) with stage 1. One patient was missing data on tumor stage. 21 patients received 5-FU based adjuvant CT, 1 patient received oxaliplatin, 15 patients received adjuvant CT- no specific info
Disease stage, n[1]	Stage 1- 16 patients (9.4%), Stage 2- 46 patients (27.1%), Stage 3- 33 patients (19.4%), and Stage 4- 75 patients (44.1%) (25 to carcinomatosis/mesentery/peritoneal, 19 to liver, 5 to lung, 2 to brain, 2 to ovary, 2 to colon, 27 not reported)

[1]Missing data : Age: 6 patients, gender:11, age at the SBA diagnosis: 11 patients, disease duration: 7 patients, survival: 72 patients, disease stage: 46 patients

*Reported values mean (range), §Only patients who underwent surgery included, CT: Chemotherapy

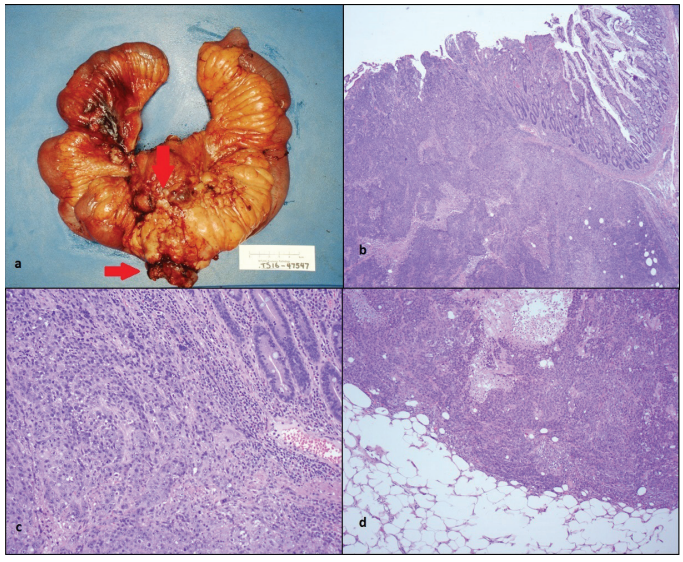

Figure 4. a) Gross image of the small bowel resection (red arrows are pointing to the tumour). b) High power view of the tumour (left) and benign small intestine (right). c) Low power view of the tumour (left) and benign small intestine (right). d) Tumour invasion of the peri-intestinal fat tissue

might also affect pathophysiology.[125] In a matched case-control study, occupational exposure to halogenated aromatic compounds and aliphatic amines, asbestos, cutting oil solvents and abrasives were shown to have a relationship with SBA development in CD.[51]

Additionally, some have suggested that medications used to control CD such as 6-mercaptopurine might contribute to cancer development when the drug is used for more than 6 months.[51,52] However, further observational studies are needed.

Presentation

These patients present with various symptoms that vary from non-specific fatigue to bleeding and complete obstruction.[69,76,83] Usually, the symptoms are subtle and indistinguishable from CD and, therefore, might be a risk factor contributing to a diagnostic delay of SBA. In some cases, the predominant initial presentation may be that of SBA rather than CD.[72,91,121] The initial findings of SBA in the setting of CD are intestinal obstruction, followed by abdominal pain, diarrhoea, weight loss and abdominal fistulae.[42,65,108] In this review, obstruction was the most common initial symptom (n=82, 59%; missing data in 77 patients). Other common symptoms were abdominal pain (n=12), anaemia-bleeding (n=11), diarrhoea (n=10) and fistulas (n=5). Additionally, the incidental finding of SBA during screening colonoscopy with retrograde ileoscopy may be the first presentation of the disease. Incidental identification of liver metastasis with biopsy has also been reported in the literature.[86,96] Free perforations in the setting of CD should arouse suspicion as to the possibility of SBA.[87,94]

SBA associated with CD is usually related to the ileum.[23,65,77,80] Palascak-Juif et al.[80] reported on 19 of 20 patients who were diagnosed with ileal SBA in the setting of CD. On the other hand, *de novo* SBA is equal throughout the proximal and distal SB.[126] In this review, there were 206 patients with one adenocarcinoma and 10 patients with two different adenocarcinomas. Among the patients with only one tumour, 154 patients (74.7%) had ileal SBA. The time from the initial CD diagnosis to the development of SBA is longer compared with other benign indications for surgery.[23] In the literature, the time lapse between diagnoses of CD and SBA ranged from 3 weeks to 15 years; in the current review, 25 patients (11.6%) were diagnosed with cancer within a month of their CD diagnosis. The median time to SBA diagnosis from CD diagnosis was 18 months (1-300 months, data on 10 patients were missing). However, it is important to acknowledge that the delay in the initial diagnosis of CD might be a factor contributing to the delay in diagnosing SBA.

Pathophysiology and Pathology

To date, the pathophysiology of SBA has not been delineated.[89] An inflammation-dysplasia-adenocarcinoma process has been suggested to affect the development of SBA in CD similar to the colorectal cancer (CRC).[71,89] In a retrospective study, similar phenotypic features of the dysplastic areas in SBA and CRC have been illustrated.[89] Recognised CRC genetic mutations such as K-Ras, APC and mismatch repair genes have been shown to be present in CRC and *de novo* SBA.[127,128,129] The presence of p53, K-Ras mutations or high microsatellite instability in the setting of CD-related SBA has also been documented in the literature.[71,115]

The incidence of sporadic SBA and carcinoid tumours has been reported to be equal in the most recent national reports.[126] However, adenocarcinoma is more common in the setting of CD than carcinoid tumour.[114] SBA is commonly diagnosed as an isolated tumour, occasionally synchronous with colonic adenocarcinomas or SB carcinoid tumours.[57,59,107,111,114] Four cases of concurrent SBA and carcinoid tumour in the setting of CD have been identified in the literature.[59,107,111,114]

Diagnosis

Commonly, the diagnosis of SBA in the setting of CD is incidental and made postoperatively. The challenge, however, is to make the diagnosis preoperatively and ensure timely extirpation.[83,91] The delays in the diagnosis were less than 2 months due to the failure of patients to report their symptoms, 8.2 months due to the absence of appropriate

diagnostic tests and 12 months due to the failure of detection on the radiological tests in patients with primary SBC.[130] Patients more commonly undergo exploratory laparotomy to treat the complications of Crohn's flair including obstruction, infection, bleeding and perforation rather than the rare diagnosis of SBA. Out of 129 patients, 64 (49.6%) were diagnosed with cancer after the surgical procedure, whereas 46 (35.6%) and 15 (11.6%) were diagnosed intraoperatively and preoperatively, respectively. Four patients (3.2%) were diagnosed at autopsy without any surgical interventions, and data were missing in 87 patients. Currently, preoperative diagnostic tools are insufficient to differentiate SBA from complicated CD. To identify malignancy preoperatively, clinicians should consider it to be the differential diagnosis, particularly in patients with new symptom onset or recurrent SB obstruction after a long-standing stable disease, fistula tracks resistant to treatment and recurrent stricture after a recent stricturoplasty (Figure 5).[45]

Imaging and Endoscopy

Imaging studies are not fully reliable to diagnose SBA in the setting of SBCD as chronic inflammation of CD maybe indistinguishable from a tumour-desmoplastic reaction.[85,131] Standard imaging techniques such as computed tomography (CT),[25] barium enema,[12,40] upper gastrointestinal and SB series,[44,47,50] magnetic resonance enterography,[86] positron emission tomography/CT and double-balloon enteroscopy[14] may be helpful in enabling the diagnosis, but these sophisticated studies may only identify a small portion of malignancies in these cases preoperatively.[47,84]

Small bowel enteroclysis and SB that follow through exams detected 90% and 33% of SB tumours in non-CD patients, respectively, but neither one is commonly utilised.[132]

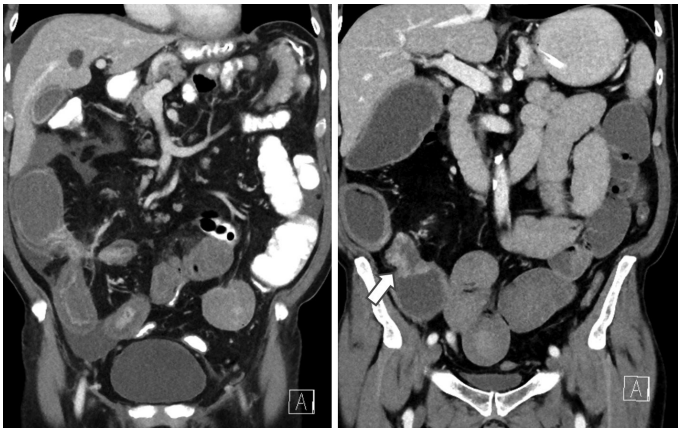

Figure 5. Patient with long-standing penetrating/fistulising CD with non-responsive bowel obstruction necessitating surgical resection. At surgery, an adenocarcinoma was found embedded in the CD changes. Although this was not prospectively recognised, in review, there are some irregular nodular mural changes in the affected region (arrow)

Conversely, CT enterography has become the imaging modality of choice, and it has been widely adopted for both the initial diagnosis and follow-up of SBA in patients with CD.[79] Although video capsule endoscopy has been used as an important endoscopic tool, the presence of CD increases the risk of capsule retention as a result of CD stricture formation.[133]

The radiological diagnosis of SBA in patients with CD has been historically challenging. Weber et al.[131] reviewed 34 CD patients with SBA, of whom 14 had preoperative imaging. They also enumerated 17 imaging features that might suggest the presence of tumours, including mass, obstruction, annular mass morphology, active inflammation with abscess cavity, perforation, abrupt luminal margins, nodularity at the mesenteric border of the mass, homogeneous enhancement patterns, bowel wall thickening, presence of penetrating disease near mass lesion or elsewhere, aneurysmal bowel dilatation and localised mesenteric stranding or metastatic disease to liver or elsewhere. Patients with malignancy at an ileocolic anastomosis were excluded. Despite the abovementioned features, only 2 of the 14 cases were prospectively diagnosed.[131] In a separate study, Soyer et al.[85] reported that only five of seven SBA in CD patients could be retrospectively identified on CT enterography. They listed SB mass, heterogeneous strictures, high-grade obstruction or irregular and circumferential bowel wall thickening as suggestive features of identifying SBA.[85] Both reports highlighted the overlap of imaging findings in patients with long-standing CD with or without superimposed adenocarcinoma. The ability to use diffusion restriction as an imaging parameter allowed for the prospective diagnosis of two SBAs in CD.[86] However, both cases were described as bulky masses that would have likely been diagnosed by other modalities such as CT or barium studies.

Treatment and Prognosis

Therapy options are limited, and surgery is the main stay of management when feasible. Locoregional SBA is treated with wide resection and lymph node dissection. Lymph node spread is commonly seen in patients with jejunal or ileal adenocarcinomas, which are the locations frequently observed in SBA in the setting of CD.[47,134] For tumours confined in the terminal ileum, adequate SB margins plus a formal right colectomy are indicated to properly remove the tumour and lymph node basin. Adjuvant chemotherapy with different regimens has been recommended and used in patients with positive lymph nodes, but a recent retrospective study reported no statistically significant difference in disease-free survival and overall survival with or without neoadjuvant therapy.[124] The rationale behind using adjuvant chemotherapy to treat SBA is mainly to prevent recurrent

disease, akin to the management principles of the colonic adenocarcinoma. Small numbers preclude prospective clinical trials on specific regimens.[135] The literature largely consists of case reports and case series. We identified 75 patients (44.1%) with distal metastasis and 33 (19.4%) with lymph node metastasis at the time of diagnosis. The locations of distal organ metastasis and incidences are summarised in Table 1. The regimens used for adjuvant therapy showed great heterogeneity with regimens including fluorouracil (5-FU), 5-FU and leucovorin, 5-FU with lomustine, cyclophosphamide with methotrexate (in a patient where 5-FU was not available), folinic acid, 5-FU and oxaliplatin (FOLFOX), FOLFOX and cetuximab, 5-FU and steroids, and oxaliplatin, bevacizumab and capecitabine. Of 75 patients with metastasis, only 27 had information regarding adjuvant therapy. Among 62 patients (32.6%) with local disease and negative lymph nodes, 5 received adjuvant chemotherapy. Combination 5-FU and leucovorin in patients with SBA and combination capecitabine and oxaliplatin have been shown to improve the outcome in metastatic disease in a phase II trial.[136,137,138]

After the failure of 5-FU, irinotecan might be beneficial in patients with SBA in the setting of CD.[139] The prognosis of SBA in the setting of CD has been a subject of controversy in the literature. Many reports suggested worse outcomes in patients with SBA in the setting of CD compared with those in *de novo* SBA.[43,44,48,65] In young patients with distally located SBA in the presence of CD-like symptoms including abdominal pain, fatigue and weight loss, the diagnosis has been delayed, thus affecting the prognosis. When patients present with obstruction and are diagnosed with SBA, the disease is typically advanced and cannot achieve a cure with surgical treatment alone.[83] The 2-year survival rate in patients with SBA in the setting of CD was 27%, whereas the 5-year survival rate was 32.5% in patients with *de novo* SBA unrelated to CD in the SEER database.[83,126] In this review, 36.7% (18/49 patients) of patients operated for obstruction were alive at 1 year and 15.2% (7/46 patients) at 2 years. Although these percentages are lower than other studies reported in the literature, data were missing in 34 patients, which might have affected the outcomes. Palascak-Juif et al.[80] reported a median survival rate of 28 (range 7–26) months compared with that of 12 (2-74) months survival in patients with *de novo* SBA, yet half of their patients with CD received adjuvant chemotherapy, whereas none in the *de novo* group did. Weber et al.[131] reported their experience with SBA in CD and showed that 70% of patients were alive at 1 year and 52% at 2 years. However, only 73.5% of their patients were available for follow-up. In our cohort, 1-year and 2-year survival rates were 53.1% (68/128) and 30.5% (36/118), respectively, which are comparable to the data reported in the literature. Of patients, 66% were followed up with subsequent survival information. The difference in the outcomes is multifactorial, and prospective studies with matched cohorts are needed to generate evidence-based data upon to provide recommendations.

Summary

We report a meta-analysis of SBA in the setting of CD and have summarised the challenges of timely diagnosis, surgical and adjuvant treatment and survival outcomes in complicated SBA in the presence of CD. With a delay in diagnosis already present, further concern that an increase in the availability of biologics may only delay referral for timely surgery and prompt diagnosis of this highly aggressive cancer.

Peer-review: Internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.H.A., F.H.R., D.S., J.R., A.G., L.P., Concept: H.H.A., F.H.R., D.S., J.R., A.G., L.P., Design: H.H.A., F.H.R., D.S., J.R., A.G., L.P., Data Collection or Processing: H.H.A., F.H.D., L.P., Analysis or Interpretation: H.H.A., F.H.R., D.S., J.R., A.G., L.P., Literature Search: H.H.A., F.H.D., L.P., Writing: H.H.A., F.H.R., D.S., J.R., A.G., L.P.

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