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Small bowel adenocarcinomas—evolving paradigms and therapy options

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Abstract

Small bowel cancers account for 3% of all gastrointestinal malignancies. Small bowel adenocarcinomas represent a third of all small bowel cancers. Rarity of small bowel adenocarcinomas restricts molecular understanding and presents unique diagnostic and therapeutic challenges. Better cross-sectional imaging techniques and development of enteroscopy and capsule endoscopy have facilitated earlier and more accurate diagnosis. Surgical resection remains the mainstay of therapy for locoregional disease. In metastatic setting, fluoropyrimidine and oxaliplatin based chemotherapy has shown clinical benefit in prospective non-randomized trials. Although frequently grouped under the same therapeutic umbrella as large bowel adenocarcinomas, small bowel adenocarcinomas are distinct clinical and molecular entities. Recent progress in molecular characterization has aided our understanding of the pathogenesis of these tumors and holds potential for prospective development of novel targeted therapies. Multi-institutional collaborative efforts directed towards cogent understanding of tumor biology and designing sensible clinical trials are essential for developing improved therapeutic strategies. In this Review, we endeavor to outline an evidence based approach to present-day management of small bowel adenocarcinoma, describe contemporary challenges and uncover evolving paradigms in management of these rare “orphan” neoplasias.

Keywords

Small bowel cancer; small bowel adenocarcinoma; small intestinal cancer; small intestinal adenocarcinoma

Introduction

Small bowel cancers represent a group of histologically diverse tumours. Carcinoids, adenocarcinomas, lymphomas and sarcomas represent the common histological small bowel types, which have a varied distribution across the three anatomical segments of the small intestine: duodenum, jejunum and ileum (Figure 1).[1–3]Albeit rare, these small bowel cancers, with an estimated 8,810 new cases diagnosed in the USA in 2013, have an

Note: Articles published only in English were considered. No results of experiments conveyed to the authors by personal communication were included.

incidence rate comparable to chronic myeloid leukaemia, testicular cancer, Hodgkin disease and anal cancer.[4] However, small bowel cancers have received relatively little attention, both in terms of clinical cognizance and research efforts. The incidence of small bowel cancers is rising and their epidemiological landscape is changing.[1,3,5,6] Carcinoids, that comprise 44% of all small bowel cancers, currently constitute the dominant histology whereas adenocarcinomas represent approximately one-third of all small bowel cancers.[5] Discussion of all histological subtypes is beyond the scope of this Review. This Review will focus exclusively on small bowel adenocarcinomas. We summarize the existing knowledge of this 'orphan' malignancy and highlight the recent advances in our molecular understanding of the disease, together with diagnostic approaches and therapeutic options.

Small bowel adenocarcinomas

Epidemiology

Small bowel adenocarcinomas represent the second most common small bowel cancer with an annual incidence of about 7.3 cases per million worldwide.[5,6] The incidence rates vary with geographic regions, with higher rates in North America and Western Europe and lower rates in Asian countries.[7] Overall, both small bowel adenocarcinoma and colorectal cancer (CRC) are more common in developed countries compared with developing countries.[7] In the USA, it is estimated that approximately 3,250 new cases of small bowel adenocarcinomas will be diagnosed in 2013.[4,5]Although small bowel adenocarcinomas are found throughout the length of the small intestine, more than half (56%) are located in the duodenum (Figure 1).[5] There is a slightly higher proportion of small bowel adenocarcinomas in males compared with females.[8–10] The age-adjusted incidence rates of small bowel adenocarcinomas is highest among blacks (14.1/1,000,000) followed by whites (7.7) and Hispanics (6.2), and is lowest among Asians/Pacific Islanders (5.5).[11]

Small bowel adenocarcinoma and colorectal adenocarcinoma

Owing to their rarity and anatomic proximity to the large bowel, small bowel adenocarcinomas have frequently been grouped with large bowel adenocarcinomas. A number of interesting differences and similarities exist between these two cancers (Table 1).[12–17] The incidence rates for these cancers are diverging in the US, with a rising rate for small bowel adenocarcinomas and a declining rate for CRC.[5,18] However, these trends vary globally.[6,7,18] Furthermore, outcomes for small bowel adenocarcinomas have been shown to be worse than for CRC.[9,19] Earlier comparisons were deficient because they did not account for the advanced stage of small bowel adenocarcinomas, owing to inadequate lymph-node sampling in resected small bowel adenocarcinomas and anatomical difference due to partial retroperitoneal location of duodenum.[9,19] However, recent work using the Surveillance, Epidemiology and End Results (SEER) database demonstrated that even after corrections to minimize the effect of stage migration and inadequate lymph-node evaluation, small bowel adenocarcinomas have a poorer stage-stratified cancer specific survival than colon cancer.[12] Evidently, the 5-year stage-specific survival, even in stage I adenocarcinomas of jejunum and ileum with adequate lymph-node sampling is worse compared to stage I colon cancer, 81.6% versus 93.3%, $P < 0.01$, respectively.[12]

The available data suggest that small bowel adenocarcinomas arise from a similar phenotypic adenoma to carcinoma transformation as seen in CRC (Figure 2).[20,21] In a similar fashion to CRC, the risk of progression to a carcinoma is associated with size (8.3% for <1 cm versus 30% for >1cm) and histology (14.3% for tubular, 23.1% for tubulovillous and 36% for villous) of the adenoma.[20] Although the genetic alterations that underline the development of small bowel adenocarcinomas have not been as clearly delineated as in CRC, a number of notable molecular similarities and differences between the two cancers exist.[20,22] In a recent study using genomic hybridization, comparison of overall DNA copy number changes between adenocarcinomas of the colorectum, stomach and small bowel demonstrated that small bowel adenocarcinomas are more similar to CRC than gastric cancer.[23] Also, this finding held true while evaluating the duodenal samples, as nine of 10 duodenal samples were shown to cluster with CRC.[23] Studies evaluating the *HER2* oncogene have found extremely low rates of *HER2* amplification or overexpression in small bowel adenocarcinomas, a pattern that is more similar to CRC than gastric cancer.[24–26]

One of the most obvious and dramatic differences between small bowel adenocarcinomas and CRC is the approximately 50-fold lower incidence of small bowel adenocarcinomas.[4,7] This difference occurs despite the fact that the small intestine encompasses 80% of the anatomical length and 99% of the absorptive surface of the gastrointestinal tract.[27] Such a dramatic difference raises a perplexing query about tissue-specific carcinogenesis and a number of theories have been postulated, although limited experimental evidence exists to support any one explanation. This significant discrepancy probably results from the interplay between dissimilar oncogenic mechanisms, such as the markedly lower rate of mutations in the adenomatous polyposis coli (*APC)* gene in sporadic small bowel adenocarcinomas in comparison to sporadic CRC, as well as the unique microenvironment of the small intestine that protects against carcinogenic stimuli.[28–31] The low bacterial load, dilute liquid contents and relatively rapid transit time decreases the amount and duration of exposure to carcinogens in the small intestine. Additionally, higher levels of lymphoid aggregates and IgA levels in the small intestine compared to the large intestine might confer better tumour immunity and surveillance.[29]

Aetiology

Though the aetiology of most small bowel adenocarcinomas remains unclear, both familial cancer syndromes and conditions associated with increased small bowel inflammation, such as coeliac and Crohn's disease, are responsible for a subset of patients who develop small bowel adenocarcinomas.[2,9,32,33] Crohn's disease has been reported to result in a 27-fold to 60-fold increase in the risk of small bowel adenocarcinomas, and this risk correlates with duration of the disease.[34,35] Celiac disease also confers an increased risk, with one study reporting a 34-fold increase in risk for small bowel adenocarcinomas.[36] Despite the suggestion of possible common risk factors for both small bowel adenocarcinomas and CRC, based upon the strong geographical correlation of incidence rates for both these tumours, the low number of small bowel adenocarcinomas in epidemiological studies has limited the ability to make any definitive conclusions.[7] Multiple retrospective studies and two prospective studies investigating the role of alcohol, tobacco use and dietary habits as risk factors for small bowel adenocarcinomas were unable to identify consistent strong

relationships between these factors and the development of these tumours.[37–44] However, many studies have demonstrated an association between obesity and an increased risk of small bowel adenocarcinomas.[45–47]

Familial cancer syndromes

Multiple inherited syndromes such as Lynch syndrome, familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome (PJS) are associated with an increased risk of small bowel adenocarcinomas.[13,14,48] The estimated lifetime risk of development of small bowel adenocarcinomas is 2–8% and 3–5% with Lynch syndrome and FAP, respectively.[15,17] In patients with PJS, the cumulative risk of small bowel adenocarcinomas at age 65 years is 13%.[14] In patients with FAP, duodenal adenomas are present in approximately 80% of patients, and regular endoscopic screening is required in these patients, with the frequency of screening based upon the number of polyps, polyp size, polyp histology and presence of dysplasia.[49] Since a significant proportion of small bowel adenocarcinomas occur in patients with predisposing conditions, we recommend that patients presenting with a small bowel adenocarcinoma should be evaluated for a possible occult underlying condition, such Lynch syndrome and coeliac disease.

Molecular Biology

Recent efforts have improved the characterization of both the genetic and epigenetic changes that occur in small bowel adenocarcinoma (Figure 2).[23,50] Limited molecular data indicates that accumulation of genetic alterations plays a key role in the adenoma–dysplasia–carcinoma sequence in the development of small bowel adenocarcinomas (Figure 2).[51]

Wnt-APC-β-catenin pathway

The most remarkable molecular finding in small bowel adenocarcinoma is that loss-of-function mutations in the *APC* tumour suppressor gene, which is the most common event in the early development of CRC, do not play a pivotal role in the development of small bowel adenocarcinomas.[31,52] Although somatic mutations are found in 80% of sporadic CRC, only about 5% of sporadic small bowel adenocarcinomas harbour this defect.[30,31,53] In one recent study of 48 patients with small bowel adenocarcinoma, no case was found to have an APC nonsense mutation.[54]

Despite the absence of *APC* gene mutations, upregulation of the Wnt–β-catenin pathway as indicated by aberrant protein expression of β-catenin is still seen in 40–48% of small bowel adenocarcinomas.[30,52,55] Mutations in *CTNNB1* (β-catenin gene), have been reported in 14% of patients with small bowel adenocarcinoma (six out of 42 tested cases).[56–58] This mutation rate is still lower than the rate seen in CRC (26%).[59] Interestingly, the mutation spectrum is also different, with gain-of-function missense point mutations being common in CRC, but only large insertions or deletions reported in small bowel adenocarcinomas.[58,59] In a large study of 194 patients with small bowel adenocarcinomas, the presence of abnormal Wnt signalling has been correlated with a worse outcome. In 25% of cases, that had combined loss of E-cadherin and aberrant β-catenin expression, a significantly worse overall survival (13.9 months versus 49.9 months, $P<0.001$) was seen compared to cases without

aberrant expression of both proteins.[55] These cases had an increased rate of both higher grade and advanced T stage tumours.[55]

Chromosome 18q loss

Chromosome 18q harbours the 'deleted in colon cancer' (DCC) gene and *SMAD4* gene and its loss is seen in 73% of sporadic CRC and 47% of patients with small bowel adenocarcinomas.[22,57] The DCC protein seems to have a central role in cellular and extracellular matrix interactions.[60] The SMAD4 protein is integrally involved in TGF-β signaling pathway and suppresses tumour growth.[61] Although SMAD4 plays a role in a small subset of CRCs, DCC is the dominant player in tumour progression mediated by 18q loss in CRC.[62] By contrast, mutations in *DCC* are uncommon in small bowel adenocarcinomas.[51,63] Conversely, *SMAD4* mutations are seen more commonly in small bowel adenocarcinomas (30%) compared to CRC (5–16%).[64]

KRAS and P53

Mutations in *KRAS* (codon 12 and 13) have been observed in 40–60% of all sporadic small bowel adenocarcinomas and this rate is comparable to that seen for CRC.[51,65] *BRAF*V600E mutations are rare, with no mutations seen in a study of 99 cases.[30,50] Based on frequent *KRAS* mutations that occur in small bowel cancers, the RAS-RAF-MAPK pathway seems to have a role in small bowel carcinogenesis.[30] p53 overexpression and mutations are seen in 40% of small bowel adenocarcinomas indicating the pivotal role of p53 in this disease.[51] Both *KRAS* mutations and altered *p53* are seen to progressively accumulate during the adenoma–carcinoma sequence.[51]

Microsatellite instability and methylator phenotype

Microsatellite instability (MSI) and loss of mismatch-repair proteins are seen in 18–35% of small bowel adenocarcinomas compared to approximately15% of CRCs.[66–68] In small bowel adenocarcinomas, approximately 50% of cases reflect sporadic methylation of the *MLH1* gene, with one study showing *MLH1* methylation in 10 out of 20 MSI cases.[50,68] Interestingly, the majority of cases with coeliac-related small bowel adenocarcinomas demonstrate MSI with two studies reporting similar rates of 73% and 67%.[54,69] Determination of *MLH1* methylation status was conducted in one of these studies, with all 10 cases of coeliac-related MSI small bowel adenocarcinomas demonstrating *MLH1* methylation.[54] In a study aimed at evaluating CpG island methylator phenotype (CIMP) status in duodenal adenocarcinomas, CIMP was seen in 27.3% of cases.[50] CIMP-positive cases demonstrated a worse overall survival (33.9 months) than CIMP-negative cases (90.8 months), P=0.047, although this finding primarily reflected the dramatically worse outcomes seen for patients with CIMP-positive and *MLH1* unmethylated tumours.[50]

Clinical presentation and diagnosis

Small bowel adenocarcinomas have a varied and non-specific presentation and a high index of suspicion is required to make an accurate and timely diagnosis.[70] Median age of presentation of small bowel adenocarcinomas ranges from 55 to 65 years, with most cases diagnosed in the seventh or eighth decade.[8,19] Age of onset tends to be lower in patients with

predisposing conditions and familial cancer syndromes.[13,14,33,34,48] Older people (age ≥ 60 years) tend to have a higher frequency of duodenal tumours.[9,19] Owing to this non-specific presentation, the majority of patients are diagnosed with advanced-stage disease (32% stage IV, 27% stage III, 30% stage II and 10% stage I).[12]

The most common presenting symptom is abdominal pain (45–76%).[9,19,71] Other common symptoms include nausea and vomiting (16–52%), weight loss (28%), fatigue and anaemia (15–30%) and gastrointestinal bleeding (7–23%).[9,71] The most common presenting sign is anaemia and pallor, which is found in 40% of patients, with the next most common presenting symptoms being obstruction and bleeding.[9] Because of this non-specific presentation, patients usually have symptoms for a long time before diagnosis, and the mean duration of symptoms before presentation in one study was 10 months.[71]

Laboratory testing reveals nonspecific results suggestive of gastrointestinal tract bleeding (overt or occult) leading to iron deficiency anaemia. There are no specific tumour markers for the diagnosis of small bowel adenocarcinomas because of inadequate sensitivity and specificity. Both carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA 19–9) are elevated in approximately 30% and 40% patients with small bowel adenocarcinomas, and these biomarkers can be used for monitoring disease status.[72]

Immunophenotyping

Immunophenotyping of small bowel adenocarcinomas shows CDX2, CK20 and CK7 expression in 70%, 57%, and 31% cases, respectively.[67] While the most common combined cytokeratin profile is CK20+/CK7− (43%), small bowel adenocarcinomas demonstrate a much greater variability with a CK20−/CK7−, CK20+/CK7+ and CK20−/CK7+ representing 28%, 15% and 13% of tumours, respectively.[67]

Imaging

Preoperative diagnosis of small bowel adenocarcinomas is primarily made via radiographic studies and endoscopy. Although symptoms at presentation are non-specific, the major delay in diagnosis is due to the inability to order appropriate diagnostic tests or failure to make the diagnosis.[73] In one study, the average delay in diagnosis attributable to patients failing to report symptoms, physicians not ordering the appropriate diagnostic tests and radiologists failing to make the diagnosis was less than 2 months, 8.2 months and 12 months, respectively.[73] This indicates the importance of prompt and pertinent small bowel evaluation in patients with subtle, but persistent symptoms.

Conventional abdominal radiography can reveal obstruction, but otherwise has limited utility in the diagnostic work-up of small bowel adenocarcinomas. Series of studies of the upper gastrointestinal tract with either conventional small bowel follow-through or enteroclysis (contrast material infused directly into the small intestine through a nasogastric tube) can visualize primary tumours in 33% and 90% cases, respectively.[74] The major drawback of these techniques is the inability to visualize extra-luminal disease, a limitation circumvented by use of cross-sectional imaging.[75] CT and MRI based enteroclysis have an improved sensitivity and specificity for detection of small bowel tumours compared with conventional enteroclysis.[76,77] The use of CT enterography (negative oral contrast agents such as water,

polyethylene glycol or mannitol) is better tolerated than CT enteroclysis, and is able to achieve adequate small bowel distention with a similar sensitivity (93% versus 94%), but slightly lower specificity (94% versus 100%) than CT enteroclysis.[78] The role of PET–CT in diagnosing small bowel adenocarcinomas is still investigational, but could offer better detection of occult metastatic disease.[79,80]

Endoscopy

Upper endoscopy, push enteroscopy and double-balloon enteroscopy can visualize the duodenum and proximal jejunum and the entire small-bowel, respectively. However, specialized techniques such as push and double-balloon enteroscopy are time consuming, technically challenging and limited in availability.[81] Wireless video capsule endoscopy (VCE) allows non-invasive visualization of the entire small bowel lumen, has a low false-positive rate (2%) and in one pooled analysis of 24 prospective trials (n = 530 patients) comparing VCE to alternative diagnostic modalities, was found to have the lowest false-negative rate (19%).[82,83] In a large retrospective study of 562 patients who underwent VCE for a variety of reasons, small bowel tumours were identified in 8.9% of patients.[83] Based on these data, VCE has become the standard first choice endoscopic approach for patients with suspected non-duodenal small bowel cancers. The major drawback of VCE is the potential for capsule retention due to stenotic malignant and Crohn's lesions.[84] In some studies that evaluated obscure gastrointestinal bleeding, CT enterography and double-balloon enteroscopy have been shown to detect more lesions compared with VCE, and can be used in patients with stenotic lesions or patients with negative findings on VCE.[85,86]

Prognosis

Tumour stage is the single most important prognostic factor in small bowel adenocarcinomas.[9,19] Other factors associated with poor prognosis include poor differentiation, positive margins, duodenal location, male gender, black ethnicity and older age.[5] The presence of negative resection margins in curatively resected patients represents one of the strongest favourable predictors of long-term survival.[9,87–89] High lymph-node ratio (> 50–75%) and a low number of assessed lymph nodes have been significantly associated with decreased survival.[9,19,90] Two recent studies that used the SEER database have identified either ≥8 or ≥10 lymph nodes as the optimal number of assessed lymph nodes.[90,91] For patients with stage II small bowel adenocarcinomas, the 5-year disease-specific survival rates vary markedly depending upon the number of assessed lymph nodes: 44% for 0 lymph nodes, 69% for 1–7 lymph nodes and 83% for > 7 lymph nodes.[90]

Treatment strategy

Treatment of small bowel adenocarcinomas is affected by site of disease, stage at presentation, available expertise, patient comorbidities and performance status. Small bowel adenocarcinomas are staged using the combined American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system.[92] For therapeutic purposes, small bowel adenocarcinomas can be divided broadly into two groups, locoregional disease and metastatic disease (Figure 3).

Surgery for locoregional disease

Surgery is the mainstay of therapy for small bowel adenocarcinomas presenting as locoregional disease.[19] The 5-year survival of resected and unresected patients is 54% and 0%, respectively.[93] Duodenal adenocarcinomas are managed with either pancreaticoduodenectomy, performed for tumours in the first and second portion of the duodenum, or wide local excision with regional lymphadenectomy for tumours in the third and fourth portion of duodenum provided that negative margins and an adequate lymph-node evaluation can be performed. Studies have shown that an optimal wide local excision is at least equivalent to pancreaticoduodenectomy in terms of long-term survival, and that wide excision is associated with lesser post-operative morbidity and duration of hospitalization.[87,93–95] Although one study showed a survival benefit for pancreaticoduodenectomy over limited resection, this conclusion was driven by the high margin positive rate (23%) in the limited resection group.[89] Jejunum or ileal adenocarcinomas should be treated by wide local excision and regional lymph node dissection. A right colectomy is indicated for tumors involving the distal/terminal ileum.

Adjuvant therapy

The recurrence pattern after potentially curative resection of small bowel adenocarcinoma is predominantly at distant sites. In the largest study of small bowel adenocarcinomas with reported recurrence pattern, 56 of 146 patients had distant and locoregional recurrences accounting for 86% and 18% of all recurrences, respectively.[19] Even though the rates of locoregional failure are greater for duodenal adenocarcinomas, distant recurrence still predominates. A recent study of 122 patients with duodenal adenocarcinoma who underwent pancreaticoduodenectomy showed that the first site of recurrence is distant in 59% of cases, locoregional in 19% and both distant and locoregional in 22% of cases.[96]

Despite the absence of prospective randomized data elucidating the role of adjuvant therapy in small bowel adenocarcinomas, the use of adjuvant therapy has increased. Data from the National Cancer Database shows an increased use of adjuvant chemotherapy in small bowel adenocarcinomas from 8.1% in 1985 to 22.2% in 2005 ($P<0.0001$).[5,97] In all likelihood this trend reflects the poor outcome of high-risk resected small bowel adenocarcinomas, the known efficacy of systemic chemotherapy in the metastatic setting and the significant survival benefit of adjuvant chemotherapy in patients with CRC.[98] Retrospective studies have shown mixed results with regards to the benefit of adjuvant chemotherapy in treating small bowel adenocarcinomas.[9,19,89,99] There exists a need for randomized control trials to investigate the benefit of adjuvant therapy in the management of these tumours.[100] Currently the International Rare Cancers Initiative (IRCI) is planning to open a large prospective randomized trial evaluating the impact of adjuvant chemotherapy in resected small bowel adenocarcinoma termed the BALLAD study (A global study to evaluate the potential benefit of adjuvant chemotherapy for small bowel adenocarcinoma).[100,101] Despite the limited data, it is reasonable to consider the role of adjuvant fluoropyrimidine-based chemotherapy for patients with high-risk disease, such as those positive lymph nodes.

Owing to the increased risk of locoregional failure for duodenal adenocarcinomas, adjuvant fluoropyrimidine-based chemoradiation has been used for high-risk patients.[102] In a

retrospective series of 26 duodenal adenocarcinoma patients who underwent a margin negative resection, use of adjuvant or neoadjuvant fluoropyrimidine-based radiotherapy demonstrated a trend toward improved 5-year overall survival in comparison to those patients treated with surgery alone (83% versus 53%, P=0.07).[103] Of the 11 patients who underwent neoadjuvant fluoropyrimidine-based radiation therapy, a pathological complete response was seen in 2 (18%) patients.[103] In a more recent series of six patients with locally advanced unresectable duodenal adenocarcinomas, neoadjuvant therapy enabled the completion of margin negative resections in all six patients.[104] Given these results, further investigation of the use of neoadjuvant therapy for high-risk duodenal adenocarcinomas is warranted.

Metastatic disease

Systemic chemotherapy—Systemic chemotherapy has been regarded as the mainstay of treatment for patients with metastatic small bowel adenocarcinomas. Although no randomized trials have compared the use of palliative chemotherapy against best-supportive care in patients with small bowel adenocarcinomas, multiple retrospective comparisons have demonstrated the survival advantage of palliative chemotherapy (Table 2).[9,19,105–108] A combined analysis of reported outcomes from six retrospective studies showed a median overall survival of 13 months for patients receiving systemic chemotherapy compared to 4 months for those treated with best-supportive care alone (P = 0.02; Figure 4).[9,19,105–108] However, these studies are retrospective in nature, have a heterogeneous patient population and suffer from strong selection bias. Multiple agents have demonstrated activity in patients with metastatic small bowel adenocarcinomas, including 5-fluorouracil, capecitabine, oxaliplatin, cisplatin, gemcitabine and irinotecan with varying response rates (Table 2).[72,105,109–119] A weighted Spearman correlation analysis of reported outcomes in these studies reveals a moderate-to-strong positive correlation between response rate and median overall survival (Spearman r 0.62, P = 0.002) and between median progression-free survival (PFS) and median overall survival (Spearman r 0.72, P< 0.001; Figure 4).This analysis indicates that PFS is a stronger predictor of patient survival compared to response rate, although further validation of such end points as surrogates for overall survival is needed.

Although no randomized trials have compared the efficacy of different chemotherapy regimens in patients with small bowel adenocarcinomas, four prospective studies have been conducted with three using fluoropyrimidine and oxaliplatin as the backbone chemotherapy (Table 2). These studies demonstrate similar activity with response rates of 39–52% and median PFS of 7.8 to 11.3 months. Based on these findings, the standard frontline therapy for small bowel adenocarcinomas should consist of either CAPOX (capecitabine and oxaliplatin) or FOLFOX (5-fluorouracil, leucovorin and oxaliplatin).[110,112] As second-line therapy, FOLFIRI (5-fluorouracil, leucovorin and irinotecan) has been evaluated after failure of 5-fluorouracil and platinum-based chemotherapy in two studies, and showed a disease control rate of approximately 50% and a median PFS of 3–5 months.[113,114] At present, the role of targeted agents, such as bevacizumab, regorafenib or anti-EGFR monoclonal antibodies, which are commonly used in CRC, has not been established in small bowel adenocarcinomas. Notably both VEGF (91%) and EGFR (71%) are highly expressed in small bowel adenocarcinomas and *KRAS* mutations are similar for small bowel

adenocarcinomas and CRCs.[65,67] Anecdotal case reports have described the activity of anti-EGFR therapy (such as cetuximab), in patients with *KRAS* wild-type small bowel adenocarcinomas.[120,121] A number of ongoing studies are exploring anti-EGFR agents in small bowel adenocarcinomas (Table 3).

Surgery—The primary tumour site in small bowel adenocarcinomas can cause significant morbidity from obstruction (nausea, vomiting and poor nutrition) and bleeding. Palliative surgery (segmental resection or bypass) or radiation therapy (especially for duodenal primaries) might be necessary in cases with unresectable or metastatic disease.[8] For patients with duodenal adenocarcinoma who are not surgical candidates, self-expandable metal stents can be considered for relief of bowel obstruction.[122] Data concerning metastatectomy in small bowel adenocarcinomas are limited. Although two studies evaluating hepatic resection in patients with oligometastatic liver disease have demonstrated improved survival, the number of patients with small bowel adenocarcinomas ($n = 30$) were too few to draw any robust conclusions.[123,124] Patient selection based on clinical behaviour of the disease and available surgical expertise plays a critical role in this decision.

Conclusions

Small bowel adenocarcinomas are rare malignancies. Even though small bowel adenocarcinomas are morphologically similar to CRC adenocarcinomas, they represent a distinct clinical, pathological and molecular entity. Dysregulation of the Wnt/β-catenin pathway, TGF-β signalling and cell-cycle regulation is integrally involved in molecular pathogenesis of these tumours. Inadequate evidence, non-specific symptoms and lack of clinical awareness and experience hamper deliver of optimum care to patients with this rare cancer. Surgery and systemic chemotherapy is the mainstay of therapy for locoregional and metastatic disease, respectively. Surgical resection with adequate lymph-node sampling is critical for long-term survival in resectable disease. Despite limited data on efficacy of adjuvant chemotherapy, its use in patients with high-risk disease should be discussed. Participation in clinical trials should be strongly encouraged.

With an increased understanding of the molecular biology of small bowel adenocarcinomas, the prospect of using targeted therapy in these tumours has become a distinct possibility. However, further work to establish valid preclinical model systems to enable the exploration of various therapeutic interventions is needed. As large-scale phase III randomized trials are problematic owing to the rare incidence of these tumours, multi-institutional collaborative initiatives and innovative clinical trial designs are vital to improve care for patients with this orphan malignancy.

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KEY POINTS

- Small bowel tumours are rare cancers and their incidence worldwide is increasing
- Clinical presentation is non-specific and specialized diagnostic modalities, such as enteroclysis, enterography, enteroscopy and video-capsule endoscopy are needed for early diagnosis
- Surgery is the mainstay treatment for locoregional disease and the benefit from adjuvant chemotherapy is unclear
- Systemic fluoropyrimidine and oxaliplatin-based chemotherapy has shown clinical benefit in metastatic disease
- Recent molecular characterization efforts have revealed distinct molecular biology and pathogenesis compared to colorectal cancers
- Large-scale collaborative research efforts are necessary to improving our knowledge regarding the management of these uncommon tumours

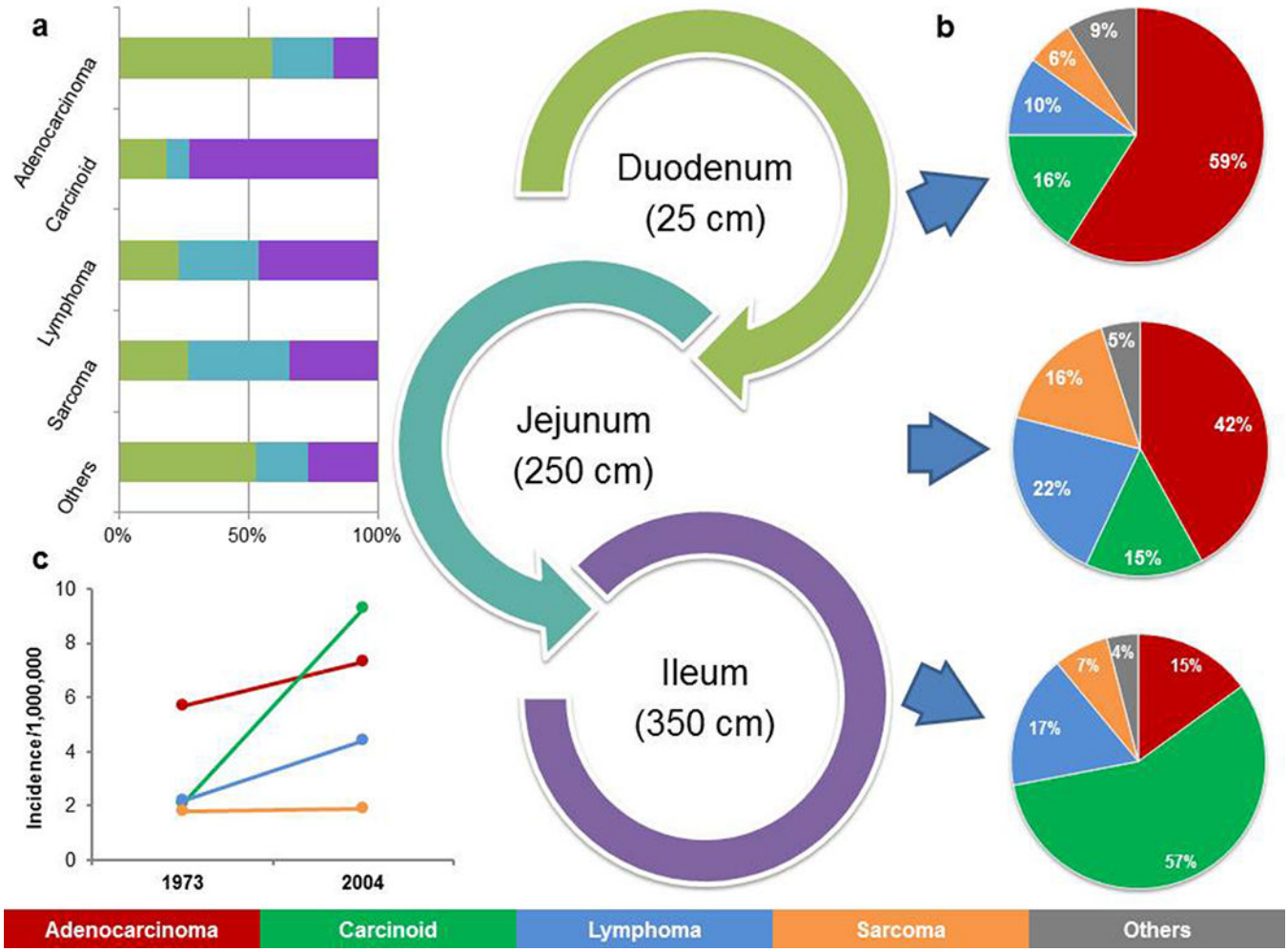

Figure 1 |.

Epidemiology of small bowel tumours from the National Cancer Data Base (NCDB) (1985–2005) and U.S. Surveillance, Epidemiology and End Results (SEER) (1973–2005) cohorts and Connecticut Tumor Registry 1980–2000.[2,3,6] **a |** Majority of adenocarcinomas and carcinoids are seen in the duodenum and the ileum, respectively. **b |** Incidence of small bowel tumours, especially carcinoids, adenocarcinomas and lymphomas has increased in the past few years. **c |** The proportion of histological tumour subtypes found in the small bowel varies depending on the anatomic location of the small bowel.

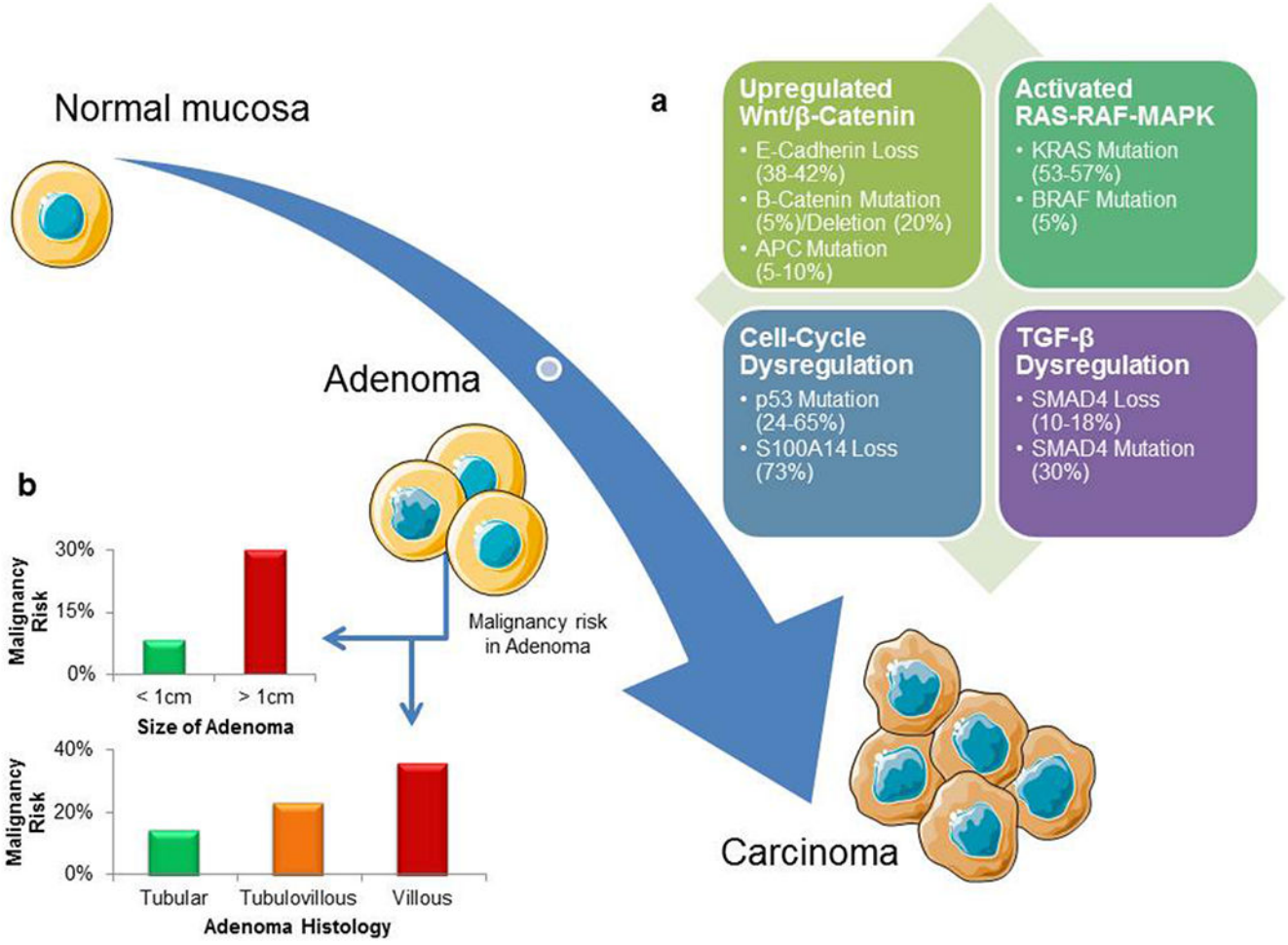

Figure 2 |.

The adenoma–carcinoma sequence in small bowel adenocarcinomas. **a** | A number of molecular alterations are implicated in small bowel carcinogenesis. **c** | Risk of progression of adenoma to malignancy depends on the tumour size and histology.

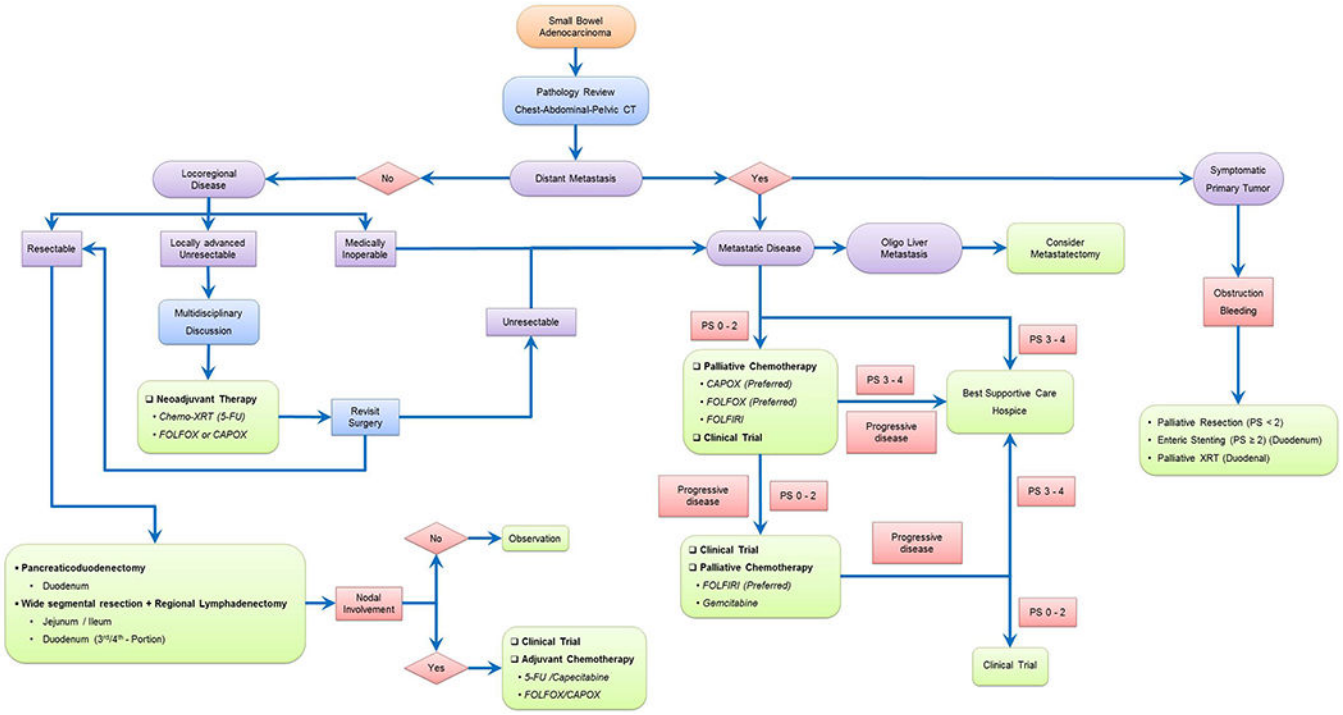

Figure 3|.

Schematic management of patients with small bowel adenocarcinomas. Treatment strategy depends on disease stage and involves en-bloc resection for locoregional disease and systemic chemotherapy for metastatic disease. All current recommendations are based on case series, retrospective reviews or non-randomized prospective trials because of an absence of any randomized data. Abbreviations: PS, performance status; 5-FU, 5-fluorouracil; FOLFOX, 5-FU, leucovorin and oxaliplatin; CAPOX, capecitabine plus oxaliplatin; FOLFIRI, 5-FU, leucovorin and irinotecan; KRAS-WT, KRAS wild-type; XRT, radiation therapy.

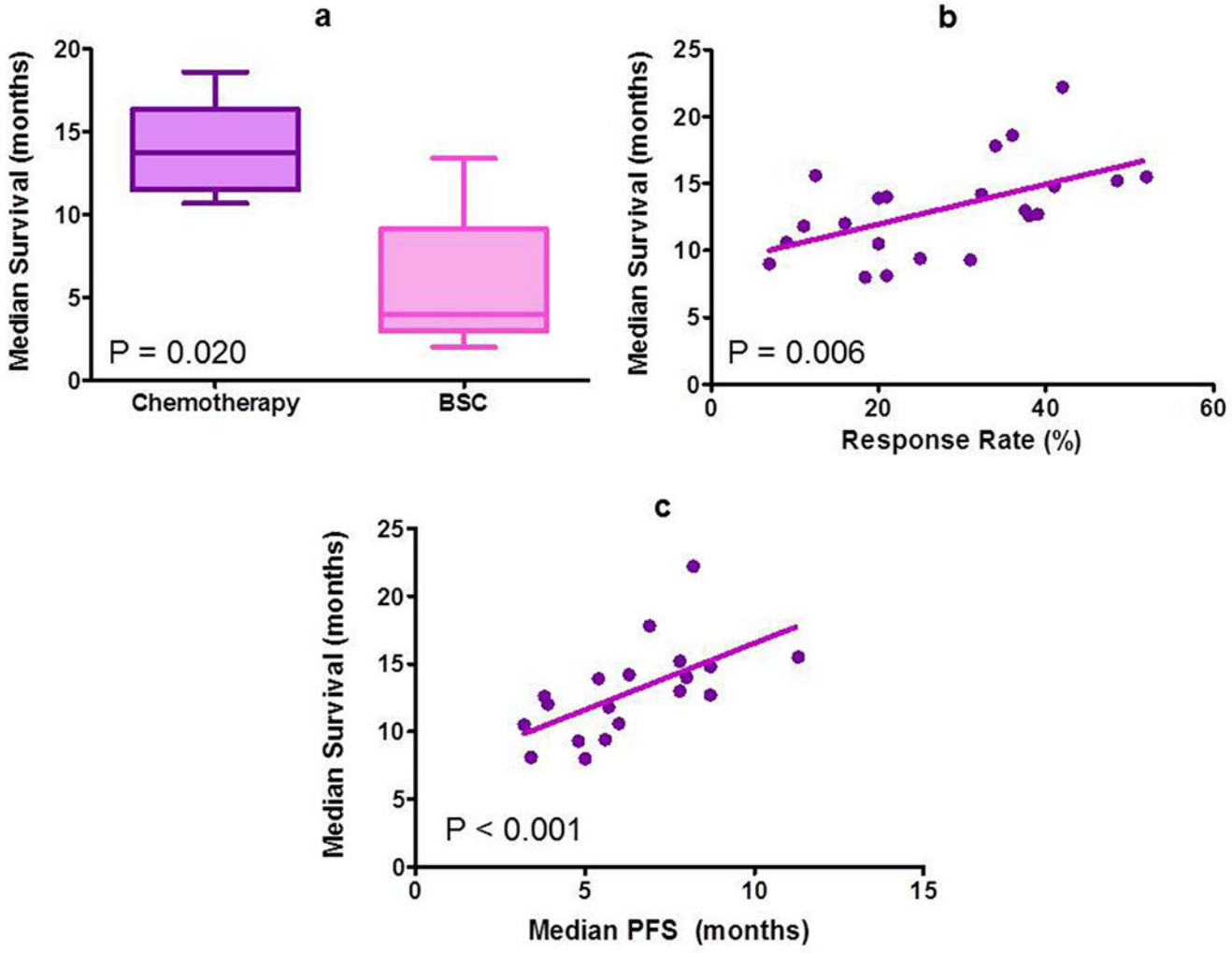

Figure 4 |.

Role of chemotherapy in metastatic small bowel adenocarcinoma. **a |** Median overall survival is significantly more in patients receiving palliative chemotherapy (13.7 months) as compared to best-supportive care (4.0 months) alone. **b |** Response rate to palliative chemotherapy show moderate correlation with median overall survival in metastatic small bowel adenocarcinomas. **c |** Median progression-free survival on palliative chemotherapy correlates strongly with median survival in metastatic small bowel adenocarcinomas.

Table 1 |

Comparison between small bowel and large bowel adenocarcinoma

Factors	Small bowel adenocarcinomas	Large bowel adenocarcinomas
Estimated new cases in 2013 (USA)	3,250	142,820
Age-standardized incidence	Rising (+ 1.47% per year)	Falling (− 1.24% per year)
Age-standardized mortality	Stable	Decreasing (−2.31% per year)
Median age at diagnosis	67 years	71 years
Gender distribution	Male > female	Male > Female
Race distribution	Blacks > whites	Blacks > whites
Stage IV presentation	32%	20%
High-grade tumours	33%	21%
APC mutation rate	7–13%	60–68%
Lifetime cancer risk with Lynch Syndrome	2–8%	39–70%
65-year cumulative risk with PJS	13%	39%
Lifetime cancer risk with FAP	3–5%	100%
IBD most associated	Crohn’s disease	Ulcerative colitis

Abbreviations: FAP, Familial adenomatous polyposis; IBD, inflammatory bowel disease; PJS, Peutz-Jeghers syndrome.

Table 2 |

Studies evaluating role of palliative chemotherapy in metastatic small bowel adenocarcinoma

Reference	Year	Trial type	*n*	Chemotherapy regimen	RR (%)	TTP PFS (months)	Median OS versus BSC (months)
McWilliams	2012	Phase II (NCCTG)	23	CAPOXIRI	39.0	8.7	12.7
Xiang	2012	Phase II (China)	33	FOLFOX	48.5	7.8	15.2
Overman	2009	Phase II (MDACC)	25	CAPOX	52.0	11.3	20.4
Gibson	2005	Phase II (ECOG)	38	FAM	18.4	5.0	8.0
Tsushima	2012	Retrospective	60	5-FU alone	20.0	5.4	13.9
			17	5-FU + cisplatin	38.0	3.8	12.6
			22	FOLFOX	42.0	8.2	22.2
			11	FOLFIRI	25.0	5.6	9.4
			22	Various Agents	21.0	3.4	8.1
Koo	2011	Retrospective	81	5-FU based	11.1	5.7	11.8 vs 4.1; *P*<0.001
Zhang	2011	Retrospective	34	FOLFOX/CAPOX	32.3	6.3	14.2
Zaanan	2010	Retrospective	28	FOLFIRI	20.0	3.2	10.5
Zaanan	2010	Retrospective	38	FOLFOX	34.0	6.9	17.8
			11	FOLFIRI	9.0	6.0	10.6
			13	5-FU + cisplatin	31.0	4.8	9.3
Halfdanarson	2009	Retrospective	165	Various agents	NR	NA	15.5 vs 3.3; *P*<0.001)
Overman	2008	Retrospective	29	5-FU + platinum	41.0	8.7	14.8
			51	Various agents	16.0	3.9	12.0
Czaykowski	2007	Retrospective	37	Various agents	12.5	NA	15.6 vs 7.7 *P*=0.08)
Fishman	2006	Retrospective	105	Various agents	36.0	NA	18.6 vs 13.4 *P*= 0.03)
Locher	2005	Retrospective	20	5-FU + platinum	21.0	8.0	14.0
Dabaja	2004	Retrospective	49	NR	NR	NA	12.0 vs 2.0 *P*=0.02)
Crawley	1998	Retrospective	8	5-FU based	37.5	7.8	13.0
Ouriel	1983	Retrospective	14	5-FU based	NR	NA	10.7 vs 4.0; NR
Jigyasu	1984	Retrospective	14	Various agents	7.0	NA	9.0

Abbreviations: N, total number of patients; RR, response rate; OS, overall survival; BSC, best supportive care; NR, not reported; NA, not applicable; 5-FU, 5-fluorouracil; FAM, 5-FU + doxorubicin + cisplatin; CAPOX, capecitabine + oxaliplatin; CAPOXIRI, CAPOX + irinotecan; FOLFOX, 5-FU + leucovorin + oxaliplatin.

Table 3 |

Current clinical trials for advanced small bowel adenocarcinoma

Identifier	Phase	Tumour type	*n*	Therapy line	Agent
NCT00354887	II	SBAC + ampullary	30	1st	CAPOX + bevacizumab
NCT00433550	II	SBAC	33	1st	Capecitabine/oxaliplatin/irinotecan
NCT01202409	II	SBAC + ampullary	20	1st	CAPOX + panitumumab (*KRAS* wildtype)
NCT00987766	1b	Duodenal + ampullary	22	1st	GEMOX + erlotinib
NCT01730586	II	SBAC	10	≥ 2nd	Nab-paclitaxel

Abbreviations: N, total number of patients; SBAC, small bowel adenocarcinoma; CAPOX, capecitabine + oxaliplatin; GEMOX, gemcitabine + oxaliplatin.