Localized Small Bowel Adenocarcinoma Management

Subjects: Oncology

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Small bowel adenocarcinoma is a rare but aggressive disease that requires peri-operative treatment. Due to its rarity, there is little data on small bowel adenocarcinoma treatment, and most recommendations come from expert agreements or analogies to the management of colon cancer.

Keywords: small bowel adenocarcinoma ; duodenal cancer ; chemotherapy ; chemoradiotherapy

1. Introduction

Small bowel cancers are rare diseases, accounting for approximately 5% of gastrointestinal cancers (Siegel, 2020) [1], with the predominance of small bowel adenocarcinoma (SBA), most commonly located in the duodenum (Locher, 2018) [2].

Studies based on the French prospective clinico-biological database (called NADEGE cohort) have shown that most patients have localized disease at diagnosis and that the associated prognosis is worse than that in colon cancers (Aparicio, 2020) [3]; this finding is consistent with that of a previous study (Howe, 1999) [4]. After a median follow-up of 54 months, the 5-year overall survival rate was 87.9%, 78.2% and 55.5% for disease stages I, II and III, respectively (Aparicio, 2020) [3].

Predisposing diseases are familial adenomatous polyposis, Lynch syndrome, Peutz-Jeghers syndrome, Crohn's disease and celiac disease (Green PH 2002) [5]. In the NADEGE cohort, the prevalences of an associated predisposing disease were 8.7%, 6.9%, 1.7%, 1.7% and 0.6% for Crohn's disease, Lynch syndrome, familial adenomatous polyposis, celiac disease and Peutz-Jeghers syndrome, respectively (Aparicio T., 2020) [3].

Given its rarity, there is little evidence on the treatment of SBA; in fact, most recommendations come from expert agreements or from analogies to the management of colorectal cancer (CRC), requiring multidisciplinary discussions per case (Locher, 2018) [2]. Most studies on the treatment of localized SBA are retrospective or derived from large databases such as the National Cancer Database or Surveillance, Epidemiology, and End Results (SEER) database. These large retrospective epidemiological databases account for tumor location (duodenum, jejunum and ileum); however, recent studies have shown that tumors that share a location remain heterogenous and that each tumor is associated with a different prognosis and requires a tailored approach to therapy, including surgery (Chow, 1996; Howe, 1999; Gustafson, 2008) [4][6][7].

2. Surgical Approaches

According to international guidelines, surgical resection of SBA requires a thorough exploration of the abdominal cavity due to the high risk of peritoneal invasion. Surgical treatment is based on the principle of a monobloc resection of the tumor with a distal and proximal margin of at least 5 cm. It also requires a healthy circumferential margin and a monobloc removal of the adjacent mesentery with the localization of the vascular pedicle (distal lymph nodes) and an adequate locoregional lymph node dissection (Locher, 2018; Benson, 2019) [2][8].

In contrast to pancreatic ductal adenocarcinomas, which diffusely infiltrate the surrounding soft tissues, the extension of duodenal adenocarcinomas into adjacent tissues is usually localized, and tumor-free resection margins can be obtained without resecting adjacent organs or soft tissues (Sohn, 1998; Brücher, 2001; Abrahams, 2002) [9][10][11].

Technically, resection of the primary and investing mesentery allows the removal of both primary cancer and regional nodes at risk of metastasis and provides important information for staging. However, adequate mesenteric resection may be limited by the proximity of local lymph nodes or the location of a primary tumor within the superior mesenteric artery. The optimal number of regional lymph nodes required for adequate staging is subject to debate (Overman, 2010;

Overman, 2012; Tran, 2015; Wilhem, 2016) [12][13][14][15]. However, the National Comprehensive Cancer Network (NCCN) guidelines recommend the use of at least eight regional nodes (Benson, 2019) [8].

The type of resection depends on tumor location (Locher, 2018; Benson, 2019) [2][8]. For localized cancers of the jejunum or ileum, segmental bowel resection with localized lymph node dissection is often performed. The anatomical proximity of the duodenum to the cephalic pancreas makes the surgical management of duodenal cancers different from that of cancers at other intestinal locations.

Cephalic duodeno-pancreatectomy (CDP) is required for tumors involving the second portion of the duodenum and for those that invade the ampulla of Vater or the pancreas. For tumors involving the first, third and fourth portions of the duodenum that do not involve the pancreas or the ampulla of Vater, the evidence on the need for CDP versus segmental duodenal resection remains controversial. A recent study of 1611 duodenal cancer patients showed that radical resection by CDP was not associated with improved prognosis compared to segmental duodenal resection (Cloyd, 2015; Platoff, 2020) [16][17]. In contrast, lymph node staging improved after radical resection by CDP. A total of eight studies (Kaklamanos, 2000; Tocchi, 2003; Kelsey, 2007; Han, 2008; Cecchini, 2012; Onkendi, 2012; Cloyd, 2015; Jiang, 2016) [16][18][19][20][21][22][23][24] comparing the survival of patients treated with CDP or segmental resection were included in a meta-analysis. These studies reported no significant difference in survival when comparing outcomes of segmental resection to those of CDP (Meijer, 2018) [25]. Two studies reported more overall and more positive lymph nodes removed with CDP than with segmental resection (Cloyd, 2015; Onkendi, 2012) [16][23]. However, these findings are inconsistent with those of another study, which showed no survival differences (Kaklamanos, 2000) [18].

Overall, most studies, despite small samples, show similar results for CDP and segmental resection. A recent study has demonstrated better recurrence-free survival (RFS) (39 months vs. 13 months) after CDP than after segmental resection (Colina, 2020) [26].

Moreover, SBA is often associated with several predisposing conditions: Crohn’s disease, celiac disease, Lynch Syndrome and familial adenomatous polyposis, among others. However, while these predisposing conditions may have implications in terms of screening for patients who have not yet developed small bowel cancer, there are no veritable implications in terms of surgical or adjuvant procedures. In particular, due to a lack of literature, there is no indication for prophylactic surgery for small bowel cancers.

3. Medical Approaches

SBA relapse tends to be metastatic, with one retrospective study reporting that distant and locoregional relapse accounts for 86% and 18% of all recurrences, respectively (Dabaja, 2004) [27]. Although a higher rate of local recurrence is observed for duodenal malignancies, distant metastatic relapse remains predominant (Bakaeen, 2000) [28]. These findings suggest a need for (neo)adjuvant systemic therapy.

3.1. Neoadjuvant Chemo-Radiotherapy

According to international guidelines (Locher, 2018; Benson, 2019) [2][8], in the absence of distant metastasis, primary surgery is indicated for resectable localized tumors unless posterior invasion impairs R0 tumor resection. In this case, preoperative treatment may be required to make the lesion resectable (expert opinion). For example, in one study, 9% of patients were offered neoadjuvant treatment of heterogenous modalities, with radiation therapy delivered in 14% of the cases (Colina, 2020) [26].

There is limited evidence to support the role of neoadjuvant chemotherapy or chemo-radiotherapy (CRT) in locally advanced SBA. In a study based on the National Cancer Database, neoadjuvant chemotherapy was associated with better overall survival in the “proximal” (duodenum) cohort ($p < 0.01$), while adjuvant chemotherapy was associated with better overall survival in the “proximal” ($p < 0.01$) and “distal” (jejuno-ileal) cohorts ($p < 0.01$), compared to surgery alone. These results may be due to differences in biological and pathological characteristics between duodenal and jejuno-ileal tumors, as proximal tumors are more likely than distant tumors to have a higher grade (Tiffany C. Lee, 2020) [29]. A meta-analysis of five studies ($n = 117$) revealed no impact of preoperative chemotherapy or CRT on overall survival (Meijer, 2018) [25]. Kelsey et al. evaluated neoadjuvant CRT and surgical outcomes in a case series of locally advanced duodenal adenocarcinoma. Two (18%) patients had a complete pathological response (Kelsey, 2007) [20]. Meanwhile, all patients treated with surgery alone had invasive lymph nodes postoperatively, whereas none of the patients who received preoperative CRT had pathological lymph node positivity, suggesting the potential locoregional downstaging benefits of CRT (Kelsey, 2007) [20]. A separate study has shown that, among 10 patients with locally advanced disease, most (90%) initially unresectable tumors became resectable tumors (Onkendi, 2012) [30].

3.2. Adjuvant Procedures

3.2.1. Adjuvant Chemotherapy

The NCCN guidelines recommend adjuvant chemotherapy after surgery for SBA stages II and III (Benson, 2019) [8]. However, no randomized study has evaluated the benefit of this approach to overall survival (de Bree, 2018) [31]. The benefit of adjuvant therapy remains subject to debate after several small retrospective single-center studies showed some benefits of adjuvant therapy for high-risk patients. However, these findings are likely subject to selection bias; a need for varied chemotherapy regimens is likely in this context (de Bree, 2018) [31].

A retrospective study of 241 patients with resected SBA (stages I–III) treated over 22 years revealed that 35% of the patients received adjuvant chemotherapy. Among those treated with this modality for stage III SBA, the median overall survival was 33.8 months, compared with 24.7 months in patients treated without it ($p < 0.01$) (Huffmann, 2020) [32]. No benefit was demonstrated in patients with stage I or II diseases. FOLFOX and 5FU were provided to most patients. Other less commonly used treatments included capecitabine/oxaliplatin, capecitabine alone and irinotecan alone. Compared to no therapy at all, FOLFOX was associated with improved overall survival in patients with stage III disease ($p = 0.02$) (Huffmann, 2020) [32].

Furthermore, a retrospective multicenter study of the Asian population revealed that “combined” adjuvant chemotherapy was independently associated with disease-free ($p = 0.002$) and overall survival ($p = 0.001$). Monotherapy was not superior to surgery alone in terms of overall survival (26.5 vs. 26.0 months, respectively) (Li, 2020) [33]. Meanwhile, Overman reported that adjuvant therapy affected disease-free ($p = 0.05$) but not overall ($p = 0.23$) ($n = 54$) survival. Nevertheless, the impact of adjuvant regimens was associated with the modalities they were combined with, including radiation therapy, chemotherapy, and chemoradiation. The outcomes of patients treated with adjuvant chemotherapy alone ($n = 18$) were compared to those of patients who received no adjuvant therapy, revealing no impact of adjuvant chemotherapy on either disease-free ($p = 0.11$) or overall ($p = 0.36$) survival [34] (Overman, 2010). Meanwhile, the National Cancer Database studies showed overall survival benefits for proximal (duodenum; $p < 0.01$) and distal (jejunum or ileum; $p < 0.01$) tumors (Lee, 2020; Eckert, 2016) [29][35] (**Table 1**).

Table 1. Efficacy of adjuvant chemotherapy on disease-free survival and overall survival in small bowel cancers.

Author (Year)	Design	Population	Location	Stage	N (Surg/Surg + CT)	DFS (Surg vs. Surg + Adj CT)	OS
Overman (2010) [34]	Retrospective single-center	Caucasian, US	Duodenum: 67% Jejunum: 20% Ileum: 13%	I: 33% II: 38% III: 29%	54 (24/18)	No effect ($p = 0.11$)	No effect ($p = 0.36$)
Halfdanarson (2010) [36]	Retrospective medical records	Caucasian, US	Duodenum: 57%, Jejunum: 29% Ileum: 10%	I: 8% II: 29% III: 28% IV: 35%	491 (ND/34)	N/A	No effect ($p = 0.44$)
Dong Hoe Koo (2011) [37]	Retrospective	Asian, Korea	Duodenum: 65.4% Jejuno-ileum: 36.4%.	I: 15.4% II: 38.2% III: 46.2%	52 (29/23)	No effect HR 1.40; 95% CI, 0.50–3.94	No effect HR 0.80; 95% CI, 0.31–2.07
Inoue (2012) [38]	Retrospective single-center	Asian, Japan	Duodenum: 66.7% Jejuno-ileum: 33.3%	I–II: 56% III–IV: 44%	25 (13/12)	N/A	No effect ($p = 0.055$, univariate)
Khurum Khan (2015) [39]	Retrospective single-center	Caucasian, UK	Duodenum: 62.5% Jejunum: 20.8% Ileum: 14.6 NS: 2.1%	I/II: 62.5% III: 25% ND:12.5%	48 (48/27)	Median relapse-free survival: 31.1 months (95% CI: 8.0–54.3).	Median OS: 42.9 months

Author (Year)	Design	Population	Location	Stage	N (Surg/Surg + CT)	DFS (Surg vs. Surg + Adj CT)	OS
Donat Duerr (2016) [40]	Retrospective single-center	Caucasian Swiss/Canada	Duodenum: 48% Jejunum: 31% Ileum: 21%	I: 6% II: 27% III: 21% IV: 37% ND: 9%	76 (49/27)	No effect (p = 1)	No effect (p = 0.211)
Ecker (2016) [35]	National Cancer database	Caucasian, US	Duodenum 36% Jejuno-ileum: 43% NS: 21%	I: 3% II: 43.7% III: 53.3%	2297 (1155/1142)	N/A	Significant improvement median OS, 63.2 vs. 44.5 months (p < 0.001)
Aydin (2017) [41]	Retrospective	Turkey	Duodenum 70% Jejunum: 18% Ileum: 10%.	I/II: 44% III: 56%	78 (30/48)	No effect median DFS 48 vs. 53 months, (p = 0.41)	No effect median OS 59 vs. 64 months, (p = 0.57)
Huffman (2019) [32]	Retrospective single-center	Caucasian, US	Duodenum: 65% Jejunum 23% Ileum: 9% NS: 3%	I: 15% II: 41% III: 44%	241 (156/85)	N/A	Significant improvement for stage III with FOLFOX (p = 0.02).
Ning Li (2020) [33]	Retrospective	Asian, Chinese	Duodenum: 75.7% Jejunum: 4% Ileum: 14.9% NS: 5.4%	I: 30% II: 41% III: 29%	148 (93/55)	Significant improvement median DFS: 34 vs. 16 months (p = 0.002)	Significant improvement median OS: 40 vs. 26 months (p = 0.001)
Colina (2020) [26]	Retrospective multi-center	Caucasian, US	Duodenum: 52% Jejunum: 29% Ileum: 19%	I: 5% II: 45% III: 50%	257 (76/137)	No effect (p = 0.22)	No effect (p = 0.44)
Lee (2020) [29]	National Cancer database	Caucasian, US	“proximal” 53% “distal” 47%	I: 10.2% II: 36.8% III: 43.2% IV: 9.8%	7019 (not communicated)	N/A	Significant improvement for both proximal (p < 0.01) and distal (jejuno-ileal) tumors (p < 0.01)
Aparicio (2020) [3]	Prospective	Caucasian, French	Duodenum: 56.5% Jejunum: 24% Ileum: 19.5%	In situ: 2.5% I: 8.5% II: 33% III: 49.5% NS: 6.5%	179 (69/110)	N/A	No effect (p = 0.19)

CT: chemotherapy; DFS: disease-free survival; OS: overall survival; HR: hazard ratio; N/A: not applicable; ND: Not determined; NS: not specified; surg: surgery.

A meta-analysis of 26 studies (n = 6438) on duodenal cancer of any stage failed to show any survival benefit of adjuvant chemotherapy. In five studies that involved tumor resection, the pooled 5-year overall survival rates were comparable between groups that received adjuvant chemotherapy (n = 263) and those treated with surgery alone (n = 148) (48% vs. 46%, respectively, p = 0.70) (Meijer, 2018) [25]. In this study, 98% of patients receiving adjuvant chemotherapy were treated with an intravenous or oral fluorouracil-based regimen, either as monotherapy or in combination with platinum salts (Meijer, 2018) [25]. However, these findings should be approached with caution because different chemotherapy regimens were used, and the analysis was not stratified. Furthermore, most patients undergoing adjuvant treatment (74%) received adjuvant radiotherapy combined with chemotherapy, which precludes any adjuvant chemotherapy benefit assessment (Meijer, 2018) [25].

Another meta-analysis of 15 studies (*n* = 5986) showed no effect of adjuvant chemotherapy on survival (pooled hazard ratio (HR) = 0.89, *p* = 0.25) (Ye, 2018) [42]. Similar results were reported for 607 duodenal adenocarcinoma patients (pooled HR = 0.96, *p* = 0.77). Recurrence rates were comparable between the groups treated with and without adjuvant chemotherapy (pooled HR = 0.89, *p* = 0.48) (Ye, 2018) [42]. Nevertheless, the uptake of adjuvant chemotherapy has increased from 8% in 1985 to 24% in 2005 (Bilimoria, 2009) [43] and from 24.2% in 1998 to 43.4% in 2011, according to the National Cancer Database (Ecker, 2016) [35]. FOLFOX and CAPOX are the most common regimens, based on adjuvant colon cancer treatment recommendations and findings from phase II studies on metastatic SBA (Overman, 2009; Xiang, 2012; Nakayama, 2017) [44][45][46].

Among patients included in the prospective French NADEGE database, most patients treated between 2009 and 2012 received adjuvant chemotherapy for localized SBA, accounting for 61.5% of this patient group, including 46.3% and 84.6% of stage II and III disease cases. The oxaliplatin-based doublet chemotherapy, FOLFOX or XELOX, was the most frequent adjuvant regimen (89.9%) in contrast to fluoropyrimidine monotherapy (9.1%) (Aparicio, 2020) [3]. However, 3-year overall survival rates for stage III SBA patients were comparable to those treated with and without adjuvant chemotherapy (69.9% vs. 69.2%, respectively; *p* = 0.9496) (Aparicio, 2020) [3]. In the NADEGE cohort, patients were not randomized regarding the use of chemotherapy, which may have affected the results [3].

Finally, another study based on the National Cancer Database comparing outcomes of stage III SBA patients treated with adjuvant chemotherapy (*n* = 1142) with those of patients treated with surgery alone (*n* = 1155) revealed a significant decrease in the risk of death in the former compared to the latter group (median overall survival 42.4 vs. 26.1 months; *p* < 0.001) using propensity score matching analysis (Ecker, 2017) [35]. Some overall survival benefits associated with adjuvant chemotherapy were also observed without any significant differences in patients with stage I (158 vs. 110 months, *p* = 0.226) and II (104 vs. 79 months, *p* = 0.185), respectively (Ecker, 2016) [35].

The international randomized phase III benefit of adjuvant chemotherapy for SBA (BALLAD) trial (NCT02502370), evaluating the benefit of adjuvant chemotherapy after curative R0 surgery in stage I (excluding T1aN0), II, or III SBA is currently on-going. Patients were randomized to undergo surgery alone or surgery combined with adjuvant chemotherapy with either LV5FU2 or FOLFOX. In parallel, the CAPOX regimen is being evaluated in Japanese patients in the phase III J-BALLAD trial (UMIN000027280) conducted with the same methodology but in the Asian population (Kitahara, 2019) [47]. These trials will provide the first prospective results on the effect of adjuvant chemotherapy in localized SBA.

3.2.2. Adjuvant Chemo-Radiotherapy

Given the proximity to the pancreas, patients with SBA in the duodenum are often recommended interchangeable radiotherapy and chemotherapy strategies. A previous study reported no differences in overall survival in patients treated with adjuvant chemo-radiotherapy or chemotherapy (48.9 vs. 43.5 months, *p* = 0.669). Chemo-radiotherapy was not associated with survival benefits after positive margin surgical resection (*n* = 133; 27.6 vs. 18.5 months; *p* = 0.210) or in cases with T4 tumor stage (*n* = 461; 30.6 vs. 30.4 months, *p* = 0.844), inadequate lymph node removal (*n* = 584; 40.5 vs. 43.2 months, *p* = 0.707), lymph node positivity (*n* = 647; 38.3 vs. 34.1 months, *p* = 0.622), or poorly differentiated tumors (*n* = 429; 46.6 vs. 35.7 months, *p* = 0.434) (Eckert, 2017) [48].

The feasibility of adjuvant radiotherapy in SBA was shown in a retrospective study of 24 patients that underwent surgery for duodenal cancer by CDP. Patients treated with adjuvant chemo-radiotherapy tended to have better locoregional relapse-free survival than their counterparts (*p* = 0.07). No patient experienced grade 3 or higher toxicity during irradiation (Kim, 2012) [49]. Other studies have failed to demonstrate the survival benefits of chemo-radiotherapy versus surgery alone (Bakaeen, 2000; Kelsey, 2007; Poultsides, 2012) [20][28][50]. In fact, a previous study reported equivalent 5-year survival rates (47% vs. 48%) in patients treated with adjuvant chemo-radiotherapy and those treated with surgery alone, despite a higher rate of positive lymph nodes in patients treated with the former method than in those treated with the latter method (Poultsides, 2012) [50]. In a separate study, patients that received preoperative or postoperative chemo-radiotherapy had overall survival rates comparable to those of patients treated with surgery alone; however, pathological outcomes in the chemo-radiotherapy groups were less favorable than those in other groups (Kelsey, 2007) [20] (**Table 2**).

Table 2. Efficacy of adjuvant radio+/-chemotherapy versus surgery alone on disease-free survival and overall survival in small bowel cancer.

Author (Year)	Design	Population	Location	Stage	N (Surg/Surg + (C)RT)	DFS (Surg/Surg + (C)RT)	OS (Surg/Surg + (C)RT)
Bakaeen (2000) [28]	Retrospective single-center	Caucasian, US	Duodenum	0: 3% I: 25%% II: 37% III: 32% IV: 3%	67 (50/17)	N/A	No effect (p = 0.40)
Kim (2012) [49]	Retrospective single-center	Asian, Korea	Duodenum	I: 8.3% II:41.7% III:50%	24 (15/9)	5-year DFS rate: 64% vs. 80% (p = 0.42)	5-year OS rates: 30% vs. 47% (p = 0.38).
Kelsey (2007) [20]	Retrospective single-center	Caucasian, US	Duodenum	I: 19% II:56% III:13% IV: 6% NS: 6%	32 (16/16)	5 years DFS rate: 54% vs. 44% (p = 0.55)	5-year OS rates: 57% vs. 44% (p = 0.42).
Poultsides (2012) [50]	Retrospective single-center	Caucasian, US	Duodenum	I–II: 36.6% III: 63.4%	112 (78/34)	N/A	5-year OS rates: 47% vs. 48% (p = 0.82).

CT: chemotherapy; DFS: disease-free survival; OS: overall survival; CRT: chemoradiotherapy; DFS: disease-free survical; OS: overall survival; NS: not specified; surg: surgery.

In a larger study based on the National Cancer Database, outcomes associated with adjuvant chemo-radiotherapy were compared with those associated with adjuvant chemotherapy (n = 1028), revealing comparable survival rates in matched analysis, even in the case of pejorative histoprognostic criteria (Eckert, 2017) [48]. Furthermore, a meta-analysis of studies on adjuvant chemo(radio)therapy did not show any survival effects after adjustment for lymph node status (Meijer, 2018) [25].

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