


Bevacizumab in metastatic small-bowel adenocarcinoma: A systematic review and meta-analysis

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Abstract

Cancers of the small bowel could account for less than 5% of all gastrointestinal malignancies. Of these tumors, adenocarcinomas were the major histologic subtype and generally carried a poor prognosis. High expression of vascular epithelial growth factor (VEGF) could be seen in small bowel adenocarcinomas. A systematic review was conducted here to determine if bevacizumab, a recombinant humanized antibody against VEGF, could offer clinical benefit among patients with metastatic small bowel adenocarcinoma when combined with chemotherapy. A search for relevant published and unpublished studies was performed using PubMed, ScienceDirect, Google Scholar, the American Society of Clinical Oncology meetings library, ClinicalTrials.gov, and ISRCTN registry. Information on study design, methods, intervention, and outcomes were extracted from selected eligible studies. Methodological quality was then assessed using the Newcastle-Ottawa Scale. There was a significant improvement in mean overall survival with the addition of bevacizumab with chemotherapy versus chemotherapy alone. The use of bevacizumab with chemotherapy, likewise improved progression-free survival and objective response rate compared to chemotherapy alone. Continued use of bevacizumab beyond first progression also appeared to show benefit. The conduct of prospective controlled studies by consortia to offset the rarity of small bowel adenocarcinomas could further elucidate the efficacy of bevacizumab in the treatment of this disease.

Keywords

Bevacizumab, small-bowel adenocarcinoma, vascular epithelial growth factor, small-bowel cancer

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Introduction

Although representing 75% of the length and 90% of the surface area of the human alimentary tract, cancers of the small bowel account for less than 5% of all gastrointestinal malignancies.¹ This disease is slightly more common in men with an estimated incidence of 2.3 new cases per 100,000 population.^{2,3} The median age at diagnosis is 66 years. Among diagnosed cases, mortality increases with age at an estimated rate of 0.4 deaths per 100,000.⁴

Adenocarcinoma represents the major histologic subtype of small-bowel cancers, accounting for about 33%–40% of cases. Anatomically, more than half of adenocarcinomas of

the small bowel originates from the duodenum.^{1–3,5–7} Incidence rates vary according to geographical location, but in general, the highest rates are seen among those living in

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North America and Western Europe, while the lowest rates are observed among Asians.¹

Results of tumor phenotyping of small-bowel adenocarcinomas (SBAs) have shown that the molecular aberrations in these tumors are somewhat similar to those seen in colorectal cancers. Identified molecular phenotypes include mutations in the Wnt/adenomatosis polyposis coli (APC)/ β -catenin signaling pathway,^{1,7,8} mutation in the TP53 gene,⁹ human epidermal growth factor receptor 2 (HER2) overexpression,⁹ KRAS mutations,^{3,10,11} and alterations in mismatch repair genes. Programmed death ligand-1 (PDL-1) expression¹² and vascular epithelial growth factor (VEGF) expression³ have likewise been seen in these cancers. Identification of these phenotypes, when present, will enable the use of targeted therapy in the treatment of SBAs.

The timely diagnosis of SBAs remains to be a challenge and effective screening programs are not in place owing to the unwanted nature of this disease.¹³ SBA is often asymptomatic for extended periods.¹⁴ When symptoms arise, however, they typically present with protean symptoms that may be attributable to other conditions. Abdominal pain is the most common symptom reported by some authors. Other frequent symptoms at presentation include: nausea, vomiting, diarrhea, weight loss, fatigue, anemia, and gastrointestinal bleeding.^{7,15} Due to the prolonged latency that precedes consult, small-bowel cancer is often discovered in the context of an emergency involving gastrointestinal bleeding or bowel obstruction. Not surprisingly by this time, the patient is already in the advanced stages of the disease.¹

In general, SBAs carry a poor prognosis. Definitive treatment for locoregional disease is still surgery for resectable disease, with the primary goal of a R0 resection. Lymph node involvement is the main prognostic factor for tumors after resection. Currently, the role of adjuvant chemotherapy is unclear after resection of an SBA^{3,15} and is being investigated by an ongoing phase III study.^{16,17} For unresectable locoregional disease, palliative radiation may be offered after surgical bypass of the obstructing lesion.

On the other hand, systemic chemotherapy has been the primary treatment in metastatic SBA, and its use has been studied primarily using data gathered from retrospective studies. Results show that administration of chemotherapeutic regimens indicated for colorectal cancer provide superior outcomes versus those used for gastric cancer.^{3,15} Moreover, a number of studies have evaluated the utility of targeted agents in the treatment of metastatic SBA given alone or in combination with cytotoxic chemotherapy. These include epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), anti-EGFR monoclonal antibodies, immune checkpoint inhibitors (pembrolizumab), and bevacizumab.¹⁸

Bevacizumab, a humanized murine antibody to the protein VEGF-A, is currently approved for the treatment of metastatic colorectal cancers.¹⁹ By binding to VEGF-A, this molecule

prevents the ligand from binding to its receptor (VEGFR) resulting in antitumor effects by several mechanisms. First, it inhibits tumor neovascularization and reversal of new vessel growth. Second, it causes “normalization” of tumor blood flow by counteracting the release of vasodilatory mediators facilitated by VEGF.²⁰ Third, it directly opposes survival signals mediated by VEGF, preventing tumor proliferation.^{21,22}

Clinical question

Does the addition of bevacizumab to systemic chemotherapy confer clinical benefit to patients with metastatic SBA?

Methodology

Search strategy and study selection

A systematic review was conducted to identify studies on the benefit of adding bevacizumab in the treatment of small-bowel cancer. A search for relevant published and unpublished studies was performed using PubMed, ScienceDirect, Google Scholar, and the American Society of Clinical Oncology meetings library. The reviewers also searched for ongoing or completed trials using the ClinicalTrials.gov and the ISRCTN registries. This was done in order to determine if unpublished data exist that might be included in this analysis. In the event that such unpublished data existed, the respective investigators will be contacted to request for pertinent information. The search terms utilized were the following: small, bowel, intestine, cancer, adenocarcinoma, Bevacizumab, and anti-vascular endothelial growth factor (anti-VEGF). The last search was updated on 11 October 2018. Both free-text and medical subheadings (MeSH) terms were used in the search strategy.

Included studies involved: (1) human subjects diagnosed with small-bowel cancer (including ampullary cancer) receiving bevacizumab with or without cytotoxic chemotherapy and (2) determination of the relationship between bevacizumab use on clinical outcomes. These clinical outcomes were as follows: (1) overall survival (OS) defined as time from first treatment to death of any cause or loss to follow-up; (2) progression-free survival (PFS) defined as time from first treatment to first documentation of disease progression or death of any cause or loss to follow-up; and (3) objective response rate (ORR) defined as the sum of the complete and partial response rates.

Exclusion criteria were as follows: (1) use of non-human subjects; (2) reviews, letters, commentaries, case reports, expert opinions, and non-human studies; (3) incomplete or non-analyzable data; and (4) publication in a language other than English that did not have an English translation available. Conference proceedings, if found, were planned to be included in the analysis to minimize possible publication bias while taking into account the limitations attributed with gray literature.

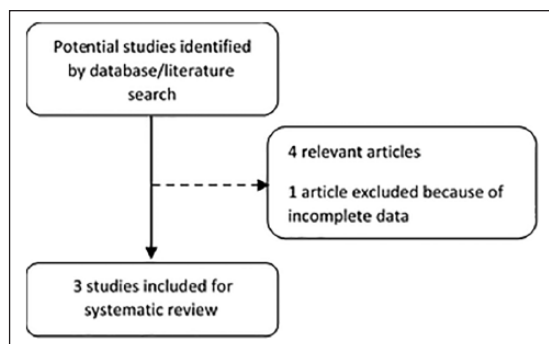


Figure 1. Study flow chart for study selection for inclusion in systematic review.

Data extraction

All searches were conducted independently by the first two investigators. These same two authors independently extracted data on the authorship and publication history of the studies included. Data on cancer studied, use of bevacizumab, concomitant cytotoxic agents used, and the outcome measures used (hazard ratio (HR) with 95% confidence interval) were also obtained from the included studies. Any discrepancy was resolved by consensus and in consultation with the third author. The fourth author provided expert supervision and resolved disagreements among the other authors.

Assessment of methodological quality

Information on study design, methods, intervention, and outcomes were extracted from selected eligible studies. Methodological quality was then assessed by the authors as poor, fair, or good using the Newcastle-Ottawa Scale for assessing non-randomized studies in meta-analysis.²³ Any form of disagreement in the assessment was resolved through consensus.

Statistical analysis

Exploratory analysis of the addition of bevacizumab in cytotoxic chemotherapy in patients with metastatic SBA was performed. The mean difference between OS from the selected eligible studies were pooled using 95% confidence interval levels. Testing for heterogeneity of the pooled results was done using Cochran's Q-test and Higgins I-squared statistic. A p value of <0.10 for Q-test was considered statistically significant, and the random-effects (DerSimonian-Laird method) model was applied to calculate the pooled mean differences. Descriptive statistics were likewise employed to describe study data, when applicable. All statistical analyses were performed using Review manager, version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark).

Results

Overview of included studies

Literature search yielded 22 citations. On scrutiny, only four articles were relevant studies.^{2,5,24,25} All four were cohort studies. No randomized controlled trials were available to date. Three studies were retrospective cohort designs while the fourth was an open-label, single-arm, single-institution phase II cohort study. This fourth study was registered in ClinicalTrials.gov and subsequently published.²⁴ Duodenal ampullary carcinomas were included as part of SBA. After scrutiny, one of the three retrospective cohort studies²⁵ was excluded because of the lack of data for the outcomes of interest in this review (no separate data for OS, PFS, and ORR for the subset of patients with SBA who received bevacizumab plus cytotoxic chemotherapy; Figure 1).

In the three included studies, a total of 46 patients received chemotherapy with bevacizumab, and 40 patients received chemotherapy alone. Patient age ranged from 27 to 83 years. Cytotoxic chemotherapy regimens used in the studies were mFOLFOX6, FOLFIRI, S-1 plus oxaliplatin (SOX), and capecitabine plus oxaliplatin (CAPOX). The characteristics of the included studies are presented in Table 1.

Assessment of risk of bias

Because the included studies were all cohort studies, we performed the assessment of risk of bias using the Newcastle-Ottawa Assessment Form for cohort studies. The assessment tool graded the studies using three categories: selection criteria, comparability of cohort, and the assessment of outcome.

The studies by Aydin et al. and Takayoshi et al. showed good methodological quality. However, the study by Gulhati et al. fared poorly in the assessment because of its lack of comparability, as the study was only a single-arm cohort (Table 2).

Publication bias is a concern in systematic reviews. Attempts have been made by the authors to identify registered trials to find studies that have been performed but not subsequently published. As stated earlier, a single trial has been identified, and this study later published. It is included in this review. In a similar vein, limiting search parameters to English language publications introduces language bias.

Outcome reporting bias is another closely related phenomenon to publication bias, wherein not all data from a study are reported in the final paper and retrospective cohort studies are prone to this problem. During the conduct of this review, authors of included studies have been contacted to request for clarification regarding outcome data. As of this writing, replies are still forthcoming. This has underpinned the decision to exclude potentially appropriate studies from this review.

Table 1. Description of the three cohort studies on the addition of bevacizumab to cytotoxic chemotherapy in metastatic small-bowel adenocarcinoma.

Study	Population	Design	Intervention	Control	Outcome
Aydin et al. ²	N=28 ECOG 0-1 Mean age: 52.4 years 57% male Median follow-up: 16.3 months	Retrospective cohort	N=12 mFOLFOX6 + Bev (5 mg/kg every 14 days) (n=6) OR FOLFIRI + Bev (5 mg/kg every 14 days) (n=6)	N=16 mFOLFOX (n=11) FOLFIRI (n=5)	PFS: 9.6 vs 7.7 months (chemo + bev vs chemo; p=0.48, 5.7-9.7) OS: 18.5 vs 14.8 (chemo + bev vs chemo; p=0.73, 15.4-21.6) ORR: 58.3% vs 43.7% (chemo + bev vs chemo; p=0.44)
Gulhati et al. ²²	N=30 patients ECOG 0-2 Mean age 63 years Median follow-up 25.9 months	Phase II Single-arm, open-label cohort	First-line CAPOX + Bev (7.5 mg/kg every 21 days)	None	PFS: 8.7 months (4.9-10.5) OS: 12.9 months (9.2-19.7) ORR: 48.3%
Takayoshi et al. ⁵	N=33 patients ECOG 0-2 median age 65 years Men 73%	Retrospective cohort	N=9 As first line: mFOLFOX6 + Bev* (n=1) CapOx + Bev (n=3) As second line**: FOLFIRI + Bev (n=3) SOX + bev (n=1) As third line: mFOLFOX6 + Bev (n=1) FOLFIRI + Bev (n=2)	N=24† The following regimens are used as first line: mFOLFOX6 (n=13) CAPOX (n=1) FOLFIRI (n=1) Irinotecan + cetuximab (n=1) 5-FU + leucovorin (n=1) S-1 (n=4) S-1 + cisplatin (n=4) Gemcitabine (n=1) Gemcitabine + S-1 (n=1) Gemcitabine + cisplatin (n=2)	OS: 21.9 vs 11.4 months (chemo + Bev vs chemo) (p=0.179)

ECOG: Eastern Cooperative Oncology Group; Bev: bevacizumab; PFS: progression-free survival; OS: overall survival; ORR: objective response rate; CAPOX: capecitabine plus oxaliplatin; SOX: S-1 plus oxaliplatin; 5-FU: fluorouracil.

*Bevacizumab dose not specified

**Two patients in the first-line chemo with bevacizumab proceeded with second-line chemotherapy with bevacizumab

†The article did not specify which of the above patients proceeded with second-/third-line chemo regimen with bevacizumab

Table 2. Assessment of risk of bias of the three studies using the Newcastle-Ottawa assessment tool.

Study	Selection		Comparability		Outcomes		Assessment	
	Representative-ness of exposed cohort	Selection of nonexposed cohort	Ascertain-ment of exposure	Outcome not present at start of study	Asses-ment of outcomes	Length of follow-up	Adequacy of follow-up	Assessment
Aydin et al. ²	*	*	*	**	*	*	*	8 (good)
Gulhati et al. ²²	*	*	*		*	*	*	5 (poor)
Takayoshi et al. ⁵	*	*	*	**	*	*	*	8 (good)

Efficacy outcomes

The researchers attempted to extract outcome measures for OS, PFS, and ORR for the three included studies. The data from the study by Gulhati et al. could not be used for pooling because of its single-arm design. Only an analysis on OS was performed—PFS and ORR data could not be pooled for analysis and thus would be summarized subsequently.

Based on two studies, there was a significant improvement in mean OS by 3.96 months with the addition of bevacizumab with chemotherapy versus chemotherapy alone (0.44, 7.48; $p=0.03$; Figure 2). Moreover, as seen in the Forest plot, there was little heterogeneity between the two pooled studies ($\chi^2=0.52, p=0.47, I^2=0\%$). The only prospective study in this review by Gulhati et al. reported a median OS of 12.9 months for the 30 patients in their study over a median follow-up of 25.9 months.

PFS was reported by Aydin et al. for 28 patients. The median PFS for their study population was 8.7 months with one- and two-year PFS rates of 11% and 0%, respectively. Across treatment groups, PFS was reported to be 7.7 months for the chemotherapy alone group compared to 9.6 months for the bevacizumab + chemotherapy group. Follow-up had a median duration of 16.3 months. Takayoshi et al. reported PFS data for all 33 patients in their study—6.0 months. Moreover, MEDIAN PFS across treatment lines for the patients who received bevacizumab could also be determined for this study. These were 15.7, 4.35, and 1.8 months for first, second, and third lines of treatment, respectively. Meanwhile, Gulhati et al. reported a median PFS of 8.7 months in their study over a median follow-up of 25.9 months.

Overall response rate was reported by Aydin et al. as 58.3% and 43.7% for bevacizumab + chemotherapy and chemotherapy-treated groups, respectively. Takayoshi et al. noted an ORR of 25% and another measure, the disease control rate, which was 60% for 20/33 patients in the first-line setting. These statistics described both those who received bevacizumab and those who did not receive this antibody. Finally, Gulhati et al. reported an ORR of 48.3% for their study.

Discussion

Due to the rarity of SBA and the challenges related to its diagnosis, there are no standard chemotherapeutic regimen available for this type of cancer to date. Treatment guidelines recommend that the regimens used for colorectal cancers, particularly oxaliplatin- and the irinotecan/CPT-11-based regimens be used, as these agents have been shown to have activity against SBA, although outcomes are still poor than colorectal cancers.^{26,27} The small number of patients with the disease also impedes the conduct of randomized controlled trials for possible chemotherapeutic agents.

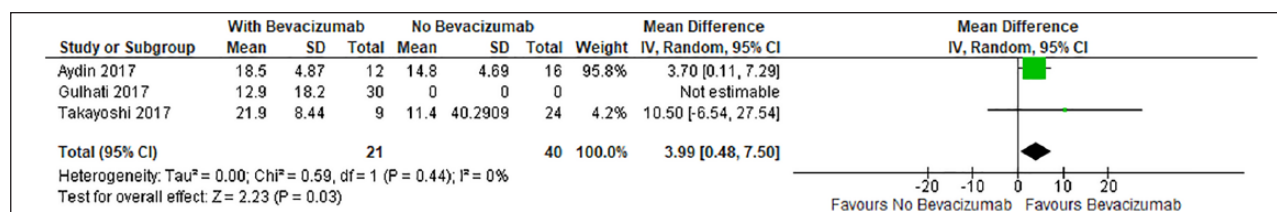


Figure 2. Forest plot for meta-analysis for overall survival with the use of bevacizumab with chemotherapy versus chemotherapy alone in metastatic small-bowel adenocarcinoma.

Bevacizumab has been suggested as a possible agent in the treatment of SBA as VEGF expression has been shown to be detectable in up to 96% of these tumors.²⁶ Thus, the use of this agent has been investigated in a number of small cohort studies. Notably, although median OS, PFS, and ORR have been shown to improve among patients receiving bevacizumab versus those who are not given this antibody, this trend fails to convincingly reach statistical significance. In addition, one of these studies²⁵ shows in a univariate analysis that treatment with bevacizumab is an important prognostic factor for improved survival time.

Three observations are worth pointing out from individual study data. First, among the patients who have been treated by Gulhati et al. are five patients with ampullary adenocarcinoma of pancreaticobiliary type. Of these, one patient exhibited a complete response, another patient had a partial response, and the remaining three experienced stable disease. This translates to a clinical benefit ratio of 100%. Meanwhile, the best outcome reported for the intestinal subtype is partial response and for the mixed subtype is stable disease. This suggests that particular tumor types might receive particular benefit when treated with bevacizumab; however, a conclusion is difficult to make from such a small population. Second, these same investigators have compared data from their bevacizumab + CAPOX-treated population to historical data from a phase II study that studied the benefit of CAPOX alone in the treatment of metastatic SBAs.²⁸ Based on this comparison, there are no differences in ORR and PFS between these two groups. Caution needs to be taken, however, in interpreting this comparison, since this is an exploratory analysis involving uncontrolled studies. The third observation is made based on data from Takayoshi et al.⁵ which demonstrated continued clinical benefit with the use of bevacizumab in metastatic SBA beyond first progression, albeit with diminishing returns. This finding was consistent with data on the use of bevacizumab in individuals with metastatic colorectal adenocarcinomas.²⁹

To the best of our knowledge, this is the first systematic review done on this topic, and we have shown that there is an improvement in OS with the addition of bevacizumab to chemotherapy by 4 months compared to chemotherapy alone. PFS and ORR have not been analyzed because of

incomplete data presented in the studies. Taken together, these findings suggest that bevacizumab may be an acceptable inclusion to the treatment armamentarium for metastatic SBA. Our pooled analysis showed little heterogeneity, but in the setting of a few non-randomized studies with small sample sizes, this result can be misleading. In addition, despite the authors' efforts to account for trials on this topic by searching trial registries, there may be unregistered clinical trials with results that may affect outcomes of interest.³⁰ Reporting bias is also a concern in this review due to the retrospective nature of some of the included studies.

Further studies, especially multicenter/consortium-based randomized trials, will contribute significantly in the validation of the efficacy of using bevacizumab in combination with chemotherapy in metastatic SBA.

Conclusion

There is currently no standard chemotherapy regimen in metastatic SBA. Bevacizumab in combination with recommended chemotherapy regimens has been reported to improve survival times in retrospective studies. This systematic review has shown an improvement in OS with the addition of bevacizumab to chemotherapy. Adding bevacizumab has also been seen to improve PFS and overall response rate. Multi-center prospective controlled studies may offset the rarity of SBAs. These can further elucidate the efficacy of bevacizumab in the treatment of this disease.

Conflict of interest

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References

- Aparicio T, Svrcek M, Zaanani A, et al. Small bowel adenocarcinoma phenotyping, a clinicobiological prognostic study. *Br J Cancer* 2013; 109(12): 3057–3066.
- Aydin D, Sendur MA, Kefeli U, et al. Evaluation of bevacizumab in advanced small bowel adenocarcinoma. *Clin Colorectal Cancer* 2017; 16(1): 78–83.
- Overman. Rare but real: management of small bowel adenocarcinoma. *Am Soc Clin Oncol Educ Book* 2013; 189–193. DOI: 10.1200/EdBook_AM.2013.33.189
- SEER. Cancer stat facts: small intestine cancer. Bethesda, MD: National Cancer Institute, <http://seer.cancer.gov/statfacts/html/smint.html> (2015, accessed 15 October 2018).
- Takayoshi K, Jusaba H, Uenomachi M, et al. Suggestion of added value by bevacizumab to chemotherapy in patients with unresectable or recurrent small bowel cancer. *Cancer Chemother Pharmacol* 2017; 80(2): 333–342.
- Kulesza J, Meszka M, Rykala C, et al. Adenocarcinoma of the small bowel—a case report. *Pol Przegl Chir* 2014; 86(6): 285–288.
- Raghav K and Overman MJ. Small bowel adenocarcinomas—existing evidence and evolving paradigms. *Nat Rev Clin Oncol* 2013; 10(9): 534–544.
- Novellasademunt L, Antas P and Li VSW. Targeting Wnt signaling in colorectal cancer. A review in the theme: cell signaling: proteins, pathways and mechanisms. *Am J Physiol Cell Physiol* 2015; 309(8): C511–C121.
- Laforest A, Aparicio T, Zaanani A, et al. ERBB2 gene as a potential therapeutic target in small bowel adenocarcinoma. *Eur J Cancer* 2014; 50(10): 1740–1746.
- Santarpia L, Lippman S and El-Naggar A. Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. *Expert Opin Ther Targets* 2012; 16(1): 103–119.
- Morkel M, Riemer P, Blaker H, et al. Similar but different: distinct roles for KRAS and BRAF oncogenes in colorectal cancer development and therapy resistance. *Oncotarget* 2015; 6(25): 20785–20800.
- Pedersen K, Smyrk T, Harrington S, et al. *Programmed death-ligand 1 (PDL-1) expression in small bowel adenocarcinomas (SBA)*. Alexandria, VA: ASCO, 2018.
- Kim JS, Park SH, Hansel S, et al. Imaging and screening of cancer of the small bowel. *Radiol Clin North Am* 2017; 55(6): 1273–1291.
- Talamonti MS, Goetz LH, Rao S, et al. Primary cancers of the small bowel: analysis of prognostic factors and results of surgical management. *Arch Surg* 2002; 137(5): 564–570; discussion 570–571.
- Nakanoko T, Koga T, Taketani K, et al. Characteristics and treatment strategies for small bowel adenocarcinoma in advanced-stage cases. *Anticancer Res* 2015; 35(7): 4135–4138.
- ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29-. Identifier: NCT02502370, PRODIGE 33 - BALLAD - Phase III Trial Investigating the Potential Benefit of Adjuvant Chemotherapy for Small Bowel Adenocarcinoma; 2015 Jul 15 [cited 2019 Jan 10];[about 4 screens]. Available from <https://clinicaltrials.gov/ct2/show/NCT02502370>
- Kitahara H, Honma Y, Ueno M, et al. Randomized phase III trial of post-operative chemotherapy for patients with stage I/II/III small bowel adenocarcinoma (JCOG1502C, J-BALLAD). *Jpn J Clin Oncol* 2018. DOI: 10.1093/jco/hyy188
- Aparicio T, Zaanani A, Mary F, et al. Small bowel adenocarcinoma. *Gastroenterol Clin N Am* 2016; 45: 447–457.
- National Comprehensive Cancer Network. Colon Cancer (Version 3), https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 17 October 2018).
- Ellis L. Mechanisms of action of bevacizumab as a component of therapy for metastatic colorectal cancer. *Semin Oncol* 2006; 33(5 Suppl. 10): S1–S7.
- Ge Y, Zhang X, Zhang J, et al. The mechanisms on apoptosis by inhibiting VEGF expression in human breast cancer cells. *Int Immunopharmacol* 2009; 9(4): 389–395.
- Perrot-Applanat M and Di Benedetto M. Autocrine functions of VEGF in breast tumor cells: adhesion, survival, migration and invasion. *Cell Adh Migr* 2012; 6(6): 547–553.
- Wells GA, Shea B, O’Connell, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
- Gulhati P, Raghav K, Shroff R, et al. Bevacizumab combined with capecitabine and oxaliplatin in patients with advanced adenocarcinoma of the small bowel or ampulla of Vater: a single-center, open-label, phase 2 study. *Cancer* 2017; 123(6): 1011–1017.
- Hirao M, Komori M, Nishida T, et al. Clinical use of molecular targeted agents for primary small bowel adenocarcinoma: a multicenter retrospective cohort study by the Osaka Gut Forum. *Oncol Lett* 2017; 14(2): 1628–1636.
- Suenaga M, Mizunuma N, Chin K, et al. Chemotherapy for small-bowel adenocarcinoma at a single institution. *Surg Today* 2009; 39(1): 27–31.
- Fishman PN, Pond GR, Moore MJ, et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. *Am J Clin Oncol* 2006; 29(3): 225–231.
- Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. *J Clin Oncol* 2009; 27(16): 2598–2603.
- Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013; 14(1): 29–37.
- Song F, Hooper L and Loke Y. Publication bias: what is it? How do we measure it? How do we avoid it? *Open Access J Clin Trial* 2013; 2013(5): 71–81.