Cochrane Library

Cochrane Database of Systematic Reviews

Adjuvant chemotherapy for small intestine adenocarcinoma (Review)

Singhal N, Singhal D

Singhal N, Singhal D.
Adjuvant chemotherapy for small intestine adenocarcinoma.
Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005202.
DOI: 10.1002/14651858.CD005202.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Adjuvant chemotherapy for small intestine adenocarcinoma

Nimit Singhal[1], Deepti Singhal[2]

[1]Medical Oncology, Royal Adelaide Hospital, Adelaide, Australia. [2]Department of ENT, The Queen Elizabeth Hospital, Woodville, Australia

Contact: Nimit Singhal, Medical Oncology, Royal Adelaide Hospital, 2/18, First Avenue, St Peters, Adelaide, South Australia, 5069, Australia. nimitsinghal@rediffmail.com.

Editorial group: Cochrane Colorectal Cancer Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 4, 2015.

Citation: Singhal N, Singhal D. Adjuvant chemotherapy for small intestine adenocarcinoma. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD005202. DOI: 10.1002/14651858.CD005202.pub2.

ABSTRACT

Background

Although the small intestine represents 75% of the length and over 90% of the mucosal surface of the alimentary tract, it is the site of only about 2% of malignant gastrointestinal tumours. Adenocarcinoma is the most common histological subtype, accounting for about 40% of all malignant small intestinal tumours. The infrequent occurrence when compared with malignancies of the stomach and colon is accompanied by non-specific clinical symptoms. The consequences are a significant delay in diagnosis and the finding of advanced, incurable disease at operation. Wide surgical resection of early lesions is the only potentially curative treatment, but it is possible only in a minority of patients. The rare nature of adenocarcinomas of the small intestine has led to a paucity of information about the benefits of adjuvant chemotherapy but there are reports of overall better survival for those patients that receive combination treatment. Most chemotherapy regimens consist of 5-fluorouracil (5-FU), alone or in combination with a variety of other agents like doxorubicin, cisplatin, mitomycin C, cyclophosphamide and oxaliplatin.

Objectives

To determine the role of adjuvant chemotherapy in the management of adenocarcinoma of the small intestine compared to another adjuvant treatment, a placebo or no other adjuvant treatment.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to 2009), EMBASE (1974 to 2009), PubMed and CINHAL using the Cochrane highly sensitive search strategy for randomised controlled trials. Additional hand searching was done by going through abstracts of major conferences like American society of clinical oncology and World GI cancer conference.

Selection criteria

Phase III randomised controlled trials comparing post-operative adjuvant chemotherapy for adenocarcinoma of the small intestine with other adjuvant therapies, placebo or no adjuvant treatment.

Data collection and analysis

No suitable trials were identified.

Main results

No studies fulfilled the inclusion criteria.

Authors' conclusions

There is a need for high quality randomised controlled trials to evaluate the effectiveness of adjuvant chemotherapy in the management of adenocarcinoma of the small intestine.

PLAIN LANGUAGE SUMMARY

Adjuvant chemotherapy for small intestine adenocarcinoma

Adenocarcinoma of the small intestine is an infrequently encountered tumour and, as such, knowledge of its clinical and pathological characteristics is limited. No suitable evidence was found to determine the role of adjuvant chemotherapy, when compared with placebo or any other or no adjuvant treatment, in the management of adenocarcinoma of the small intestine.
More research is needed.

BACKGROUND

Tumours of the small intestine, both benign and malignant, are exceedingly rare. Malignant small intestinal tumours account for 0.1 to 0.3% of all malignancies (Lowenfels 1973; Sager 1978; Coutsoftides 1979; Barclay 1983). Although the small intestine comprises 75% of the gastrointestinal length, less than 2% of gastrointestinal malignancies arise there (O'Riordan 1996; Neugut 1997; Neugut 1998; Minardi 1998; Hutchins 2001).

Primary adenocarcinoma is the most common histological subtype of carcinoma of the small intestine, constituting 25% of all small intestinal tumours and 39% of all malignant small intestinal tumours (Coit 2001). Other malignant small intestinal tumours include carcinoids, lymphomas and gastrointestinal stromal tumours, as well as metastases from melanoma, breast, lung and renal cancer (O'Riordan 1996; Neugut 1997; Minardi 1998).

Adenocarcinomas are mostly distributed proximally in the small intestine, with nearly 80% located in the duodenum or jejunum. Approximately 45% of all adenocarcinomas of the small intestine arise within the duodenum. The jejunum and ileum account for the remaining 55% of small intestinal adenocarcinomas (Coit 2001). The tumours of the small intestine do not include cancers arising from the ampulla of Vater or periampullary region. These tumours are classified separately as tumours of periampullary duodenum or carcinoma of ampulla of Vater according to TNM classification (cancer staging classification that considers T - primary tumour, N - regional lymph nodes and M - distant metastasis).

The most important known risk factor in the pathogenesis of small intestinal adenocarcinoma is previous Crohn's disease (Lashner 1992; Munkholm 1993; Persson 1994). Small intestinal adenocarcinoma is also associated with familial adenomatous polyposis, coeliac sprue, cystic fibrosis and peptic ulcer (Neugut 1998). Red meat and smoked salt-cured foods are potential dietary risk factors (Chow 1993).

The clinical presentation and diagnosis of small intestine adenocarcinoma is usually delayed, with an average delay of six to eight months from onset of symptoms (Wilson 1974; Zollinger 1986). This is primarily because small intestinal carcinomas are not amenable to endoscopic examination, especially when they are distal to the duodenum. Most commonly, patients present with signs and symptoms of obstruction, though anaemia with haemoccult-positive stools are also a frequent occurrence (Morgan 1977; Joesting 1981; Adler 1982; Lai 1988; Williamson 1983). Adenocarcinoma of the small intestine can be diagnosed through an upper gastrointestinal or small intestine oral contrast follow-through study or a computerised tomography (CT) scan. Recent data has also suggested use of capsule endoscopy in the diagnosis of such tumours. Histological confirmation can be obtained via an upper gastrointestinal endoscopy, with total duodenoscopy in duodenal lesions, but the diagnosis remains obscure for most distal lesions until a laparotomy is carried out (Williamson 1983).

Most patients with suspected or established adenocarcinoma of the small intestine undergo surgical exploration, with high resectability rates at the time of surgery. In most studies surgical intervention provides a curative resection in 40 to 65% of patients, with reported 5-year survival rates of 40 to 60% for resected tumours versus 15 to 30% for non-resected tumours (Ouriel 1984; Barnes 1994; Bauer 1994; Rose 1996). Adenocarcinomas of the first and second portions of the duodenum require pancreatoduodenectomy; whereas patients with third and fourth part duodenum lesions can undergo complete resection with segmental duodenectomy and primary anastomosis. For lesions of jejunum and ileum, wide resection of the involved segment of intestine and its corresponding mesentery is required. Lymph node metastases are frequently present at time of presentation, and thus a curative resection should generally include a systematic regional lymphadenectomy regardless of the primary tumour location (Coit 2001). Five-year survival rates after curative surgical resection have been reported as 40 to 65% in various studies. The results after non-curative resection are disappointing at 15 to 30%.

Even after curative resection approximately half of the patients will succumb to distant metastases and die of the disease. This suggests the potential for further treatment with either chemotherapy or radiotherapy to tackle micro-metastases and decrease recurrence of disease. An identical situation exists for large intestinal adenocarcinoma where curative surgical resection provides 50% 5-year survival. Adjuvant chemotherapy improves absolute survival by approximately 10 to 15% in various randomised trials. A recent trial reported 3-year disease-free survival of 78% with the use of oxaliplatin, 5- fluorouracil and leucovorin as adjuvant treatment after curative surgical resection for stage II and III large intestinal adenocarcinoma (André 2004). The role of post-operative adjuvant therapy does not seem to be clearly defined in patients with primary adenocarcinoma of the small intestine. Radiation therapy is difficult for malignancies of the jejunum and ileum because of the mobile nature of the small intestinal mesentery and the inability to localise the target field. In patients with advanced unresectable duodenal carcinoma, palliative radiation therapy may be of some benefit in controlling chronic blood loss (Brennan 1990).

Because these tumours are rare, any meaningful comment on the impact of chemotherapy in their management is difficult. There are only a few studies to date on the role of chemotherapy as an adjuvant to treatment (Jigyasu 1984; Ouriel 1984). Chemotherapy has shown responses and clinical benefit in metastatic disease, confirming the chemosensitivity of the disease. A case report of duodenal carcinoma with liver metastases showed a complete remission with 5-fluorouracil therapy, and the patient remained well 30 months after completion of therapy (William 1996). Another case report of a primary adenocarcinoma of the duodenal bulb with extensive hepatic metastases showed improvement for three years with UFTM (uracil with tegafur) chemotherapy (Okhusa 1991). Another article reported one partial response among 14 patients treated with 5-FU combination chemotherapy, accrued over 30 years (Jigyasu 1984). A report on 217 patients from the MD Anderson Cancer Center showed benefits of chemotherapy for patients with either metastatic disease or unresectable tumour. The median survival was 12 months for patients who received chemotherapy versus 2 months without (Dabaja 2004). A report of three cases of small intestine adenocarcinoma associated with coeliac disease described a safe chemotherapy regimen (FOLFOX (fluorouracil 5FU and oxaliplatin) or LV5FU2 (fluorouracil and leucovorin)) after tumour resection (Bettini 2003). Another study of 75 cases of primary malignant tumours of the small intestine stated that chemotherapy had no effect on prognosis (Zhou 1997). Similar conclusions were drawn from a series of 217 patients where adjuvant chemotherapy didn't improve survival after curative surgical resection (Dabaja 2004). The results may be due to a small number of patients treated, 59 patients being treated with adjuvant

chemotherapy. The data with regards to type of chemotherapy given was lacking. A recent retrospective review from the Mayo Clinic also failed to show benefit of adjuvant chemotherapy after surgical resection. The chemotherapy was 5- FU based but details on the exact schedule and drugs were lacking (Halfdanarson 2006). The 5-FU based chemotherapy, as a single agent or in combination with others, has been used in most case series and though the activity of 5-FU based regimens has been documented the assessment of clinical benefit is hindered by the lack of data (Kummar 2002). All the studies mentioned above are non-randomised, making it difficult to derive any meaningful conclusions.

OBJECTIVES

The primary objective of the review was to determine the role of adjuvant chemotherapy in the management of adenocarcinoma of the small intestine compared to another adjuvant treatment, a placebo or no other adjuvant treatment.
We also aimed to identify the most effective type of adjuvant chemotherapy for patients with adenocarcinoma of the small intestine.

METHODS

Criteria for considering studies for this review

Types of studies

All phase III randomised controlled trials comparing post-operative adjuvant chemotherapy to a control (no adjuvant therapy), with other adjuvant therapies or placebo were sought for the review.

Types of participants

We planned to include all patients, regardless of gender or age, who fulfilled all the criteria given below.
· Histological proof of adenocarcinoma of the small intestine.
· Patients who had undergone surgical resection of the primary tumour.

The participants in the study arm should have been allocated to chemotherapy after surgical resection of the primary tumour.

The participants in the control arm should have been receiving another adjuvant treatment or placebo or no other adjuvant treatment.

Types of interventions

The intervention under study was adjuvant chemotherapy, that is chemotherapy was given after surgical resection of the lesion.

We planned to evaluate the following comparisons:
· adjuvant chemotherapy versus another adjuvant treatment;
· adjuvant chemotherapy versus placebo;
· adjuvant chemotherapy versus no adjuvant treatment.

Types of outcome measures

The primary outcome measures of interest were:
· overall survival;
· disease-free survival.
At least one of these primary outcomes had to be reported for a study to be included in the review.

We were also interested in the number of participants that reported at least one adverse event, as a secondary outcome measure.

Search methods for identification of studies

See: the Colorectal Cancer Group search strategy.

Multiple sources were used to identify studies and the search aimed to provide a comprehensive list of studies, both published and unpublished, which could have been eligible for inclusion. An initial search was made using the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2005, Issue 4). Additional studies were searched for using MEDLINE (1966 to January 2006), EMBASE (1980 to January 2006), CINAHL (Cumulative Index to Nursing & Allied Health Literature) (1982 to Week 2 December 2005), and PubMed.

Searching took place between September 2005 and January 2006. Both medical subject headings and free-text searching were performed in order to improve the sensitivity of the searches. The search strategy given below was used to search MEDLINE (OVID), with a final search conducted on January 1, 2006.

#1 exp Chemotherapy, Adjuvant/
#2 exp Adenocarcinoma/
#3 exp Intestine, Small/
#4 #1and #2 and #3
#5 exp Neoplasms/
#6 #3 and #5
#7 exp Intestinal Neoplasms/
#8 #3 and #7
#9 exp Duodenal Neoplasms/
#10 exp Ileal Neoplasms/
#11 exp Jejunal Neoplasms/
#12 #6 or #8 or #9 or #10 or #11
#13 #1 and #2 and #12
#14 ((duoden$ or Jejun$ or Ile$ or Small Intestin$ or Small bowel $) adj5 neoplas$).tw,mp.
#15 ((duoden$ or Jejun$ or Ile$ or Small Intestin$ or Small bowel $) adj5 cancer$).tw,mp.
#16 ((duoden$ or Jejun$ or Ile$ or Small Intestin$ or Small bowel $) adj5 carcinoma$).tw,mp.
#17 ((duoden$ or Jejun$ or Ile$ or Small Intestin$ or Small bowel $) adj5 tumo$).tw,mp.
#18 ((duoden$ or Jejun$ or Ile$ or Small Intestin$ or Small bowel $) adj5 malignan$).tw,mp.
#19 ((duoden$ or Jejun$ or Ile$ or Small Intestin$ or Small bowel $) adj5 adenocarcinoma$).tw,mp.
#20 #14 or #15 or #16 or #17 or #18 or #19
#21 #1 and #2 and #20
#22 #4 or #13 or #21

For identification of randomised controlled trials, this search was combined with the Cochrane highly sensitive search strategy contained in the Cochrane Reviewer's Handbook (Alderson 2004). This strategy was modified for use with other bibliographic databases.

Handsearching
Reference lists of identified publications were scanned for additional trials. There were no language, publication year or publication status restrictions on the searches.

Data collection and analysis

Assessing trials for eligibility
All studies which were obtained by applying the above search strategies were assessed against the inclusion criteria. This was performed independently by the two review authors. Both the authors initially assessed the titles and abstracts retrieved by the search strategy to determine whether an article met the eligibility criteria. If the title or abstract left room for doubt the full text of the article was obtained to assess eligibility. A standard checklist was used to guide this process. Disagreements about study eligibility were resolved by discussion.

No suitable trials were identified for inclusion in this review.
The following methods would have been applied.

Data extraction
Data from the studies would have been independently extracted by the two review authors. Data would have been extracted so as to allow dichotomous data analysis, using standardised data forms. For any data that were missing, the review authors would write to the authors of the study requesting the missing data. Disagreements about study eligibility or data extraction would be resolved by discussion.

Quality assessment
The quality of the included trials would have been evaluated independently by the two review authors. Differences would have been resolved by discussion. Selection, performance, detection and attrition biases would have been detected from the following questions.
1) Concealment of allocation?
2) Blinding of intervention?
3) Intention-to-treat analysis?
4) Complete follow up?
5) Blinding of outcome measurement?
These questions would be answered as 'Yes', 'No' or 'Unclear'. Clarification from the primary author would be sought if the published data provided inadequate information for the review.

Data analysis
The data would be analysed as dichotomous data and the outcomes reported as relative risk (RR) and risk difference (RD) with 95% confidence intervals (CI). The studies would be assessed clinically and methodologically to assess if it was reasonable to consider combining data. If so, the fixed-effect model would be used for the analysis. If the Chi-square test for homogeneity was significant (P value less than 0.10) a random-effects model would be used. Further investigations would be undertaken to determine if the heterogeneity could be explained. An example of a factor that could potentially explain heterogeneity is any significant variation in the mean age of participants between studies.

RESULTS

Description of studies

A total of 98 studies were identified through the above electronic searching. About 40 other studies were identified by handsearching and randomly searching other sources. No randomised controlled trials were identified and, therefore, data collection and synthesis were not performed. Most studies focused on aetiology, symptoms, diagnosis, surgical treatment or prognosis. Some of the identified studies had methodologies which in part included diagnosis, treatment, recurrence and follow up but were all without control groups and were nearly all retrospective studies. All of these studies were, therefore, excluded. There was no disagreement between the review authors on the final exclusion of studies.

Risk of bias in included studies

Not Applicable.

Effects of interventions

No studies were found which satisfied the inclusion criteria for this review.

DISCUSSION

A comprehensive search strategy was used for the review. Every effort was made to identify relevant studies and no studies were excluded due to language. A large number of studies describing the aetiology, symptoms, methods for diagnosis, surgical treatment or prognostic factors were identified. While several attempts were made at searching for eligible trials it is still possible that some studies have been missed. The absence of eligible studies for review may have been due either to the restricted selection criteria or due to the absence of phase III randomised controlled trials comparing post-operative adjuvant chemotherapy to a control (no adjuvant therapy), other adjuvant therapies or placebo.

AUTHORS' CONCLUSIONS

Implications for practice

Various non-randomised studies have reported the use of 5-FU based chemotherapy for the treatment of small intestinal adenocarcinoma. The management of small intestinal adenocarcinoma has followed the management guidelines of large intestine adenocarcinoma, where large randomised trials have established adjuvant chemotherapy as the standard of care. The majority of oncologists believe that small intestinal tumours will behave in a similar way to large intestine tumours. They have similar histology, biology and prognostic factors. The authors have sent large amount of correspondence to various oncologists regarding the standard of care in the absence of randomised trials. The majority of the physicians treat small intestine adenocarcinoma in a similar way to large intestine adenocarcinoma, with adjuvant chemotherapy. There is no uniformity of chemotherapy regimens used, with the various options being combinations of 5- FU, leucovorin and oxaliplatin; capecitabine alone; or capecitabine in combination with oxaliplatin. This seems reasonable pending results of large, phase III trials evaluating the magnitude of benefit and the best combination to use. We strongly recommend enrolling all potential candidates into suitable trials.

Implications for research

The question of the role of adjuvant treatment in the management of small intestine adenocarcinoma remains open and awaits the results of phase III trials. Because these tumours are rare, such trials will require involvement of multiple centres and co-operative groups to plan and conduct them. The review authors have corresponded with various oncologists regarding the feasibility of an international trial. The American Cancer Society estimated that there were 6170 new cases of small intestine cancer in 2006 in the

USA. The adenocarcinoma will comprise 40 to 50% of these cases and half of the cancers will be confined to the bowel and eligible for surgical resection. This leaves approximately 1000 patients every year which could be eligible for an adjuvant chemotherapy trial. An important issue will be what the control group of such a randomised trial should be, since there is no current standard of care. It may be viewed as unethical to have a placebo or no treatment control group. These issues require discussion and deliberation. We have searched clinical trials registers and haven't come across any trial which is attempting to answer that question. Our discussion with gastrointestinal trials group suggested that such a trial may not be feasible because of the small numbers and the logistics of multicentre international trial. But we strongly recommend an international and multi-institutional collaborative effort to work towards answering the question.

ACKNOWLEDGEMENTS

We will like to thank Henning Keinke Andersen, Group Co-ordinator, Colorectal Cancer Group for his patience and kind support.

REFERENCES

Additional references

Adler 1982

Adler SN, Lyon DT, Sullivan PD. Adenocarcinoma of the small bowel clinical features, similarity to regional enteritis, and analysis of 338 documented cases. *American Journal of Gastroenterology* 1982;**77**:326.

Alderson 2004

Alderson. Cochrane Reviewers' Handbook 4.2.2. The Cochrane Library. Chichester Edition. John Wiley and Sons Ltd., 2004.

André 2004

Andre T, Boni C, Mounedji-Boudiaf L. Oxaplatin, fluororacil and leucovorin as adjuvant treatment for colon cancer.. *New England Journal of Medicine* 2004;**350**:2343.

Barclay 1983

Barclay THC, Schapira DV. Malignant tumors of the small intestine. *Cancer* 1983;**51**:878.

Barnes 1994

Barnes G Jr, Romero L, Hess KR, Curley SA. Primary adenocarcinoma of the duodenum: management and survival in 67 patients. *Annals of Surgical Oncology* 1994;**1**:73-8.

Bauer 1994

Bauer RL, Palmer ML, Bauer AM, Nava HR, Douglass HO Jr. Adenocarcinoma of the small intestine: 21 year review of diagnosis, treatment, and prognosis.. *Annals of Surgical Oncology* 1994;**1**:183-8.

Bettini 2003

Bettini AC, Beretta GD, Sironi P, Mosconi S, Labianca R. Chemotherapy in small bowel adenocarcinoma associated with celiac disease: a report of three cases. *Tumori* 2003;**89**(2):193-5.

Brennan 1990

Brennan MF. Duodenal cancer. *Asian Journal of Surgery* 1990;**13**:204.

Chow 1993

Chow WH, Linet MS, Mclaughlin JK, Hsing AW, Chien HT, Blot WJ. Risk factors for small intestine cancer. *Cancer Causes Control* 1993;**4**:163-9.

Coit 2001

Coit DG. Cancer of the small intestine.. In: DeVita VT Jr, Hellman S, Rosenberg SA editor(s). Cancer: Principles and Practice of Oncology. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins. 6th Edition. Philadelphia, Pa: Lippincott Williams & Wilkins,, 2001:1204-1215..

Coutsoftides 1979

CoutsoftidesT, Shibata HR. Primary malignant tumors of the small intestine. *Diseases of the Colon and Rectum* 1979;**22**:24.

Dabaja 2004

Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel. Presentation, prognostic factors and outcome of 217 patients.. *Cancer* 2004;**101**:518.

Halfdanarson 2006

Halfdanarson TR, Quevedo F, McWilliams RR. Small bowel adenocarcinoma: A review of 491 cases.. Journal of Clinical Oncology. 2006; Vol. 24:4127.

Hutchins 2001

Hutchins RR, Bani Hani A, Kojodjojo P. Adenocarcinoma of the small bowel. *Australia New Zealand Journal of Surgery* 2001;**71**:428-37.

Jigyasu 1984

Jigyasu D, Bedikian AY, Stroehlein JR. Chemotherapy for primary adenocarcinoma of the small bowel. *Cancer* 1984;**53**:23-5.

Joesting 1981

Joesting DR, Beart RW, Vanheerden JA, Weiland LH. Improving survival in adenocarcinoma of duodenum. *American Journal of Surgery* 1981;**141**:228.

Kummar 2002

Kummar S, Ciesielski TE, Fogarasi MC Kummar S, Ciesielski TE, Fogarasi MC.. Kummar S, Ciesielski TE, Fogarasi MC.Oncology (Huntingt). 2002 Oct, 16(10):1364-9, discussion 1370, 1372-3. Related Articles, Links Management of small bowel adenocarcinoma. Kummar S, Ciesielski TE, Fogarasi MC. Oncology (Huntingt). 2002 Oct, 16(10):1364-9, discussion 1370, 1372-3. Related Articles, Links Management of small bowel adenocarcinoma. Kummar S, Ciesielski TE, Fogarasi MC. Management of small bowel adenocarcinoma. *Oncology (Huntingt).* 2002;**16**(10):1364-9 and discussion 1372-3..

Lai 1988

Lai ECS, Doty JE, Irving C, Tompkins RK. Primary Adenocarcinoma of the duodenum: analysis Survival. *World Journal of Surgery* 1988;**12**:695.

Lashner 1992

Lashner BA. Risk Factors for small Bowel Cancer in Crohn's Disease. *Digestive Disease and Sciences* 1992;**37**:1179-1184.

Lowenfels 1973

Lowenfels AB. Why are small bowel tumors so rare?. *Lancet* 1973;**1**:24.

Minardi 1998

Minardi AJ Jr, Zibari GB, Aultman DF, et al. Small bowel tumors. *Journal of American College of Surgeons* 1998;**186**:664-8.

Morgan 1977

Morgan DF, Busuttil RW. Primary adenocarcinoma of small intestine. *American Journal of Surgery* 1977;**134**:331.

Munkholm 1993

Munkholm P, Langholz E, Davidsen M, Binder V. Intestinal Cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 1993;**105**:1716-1723.

Neugut 1997

Neugut AI, Marvin MR, Rella VA, Chabot JA. An overview of aenocarcinoma of the small intestine. *Oncology* 1997;**11**:529-536.

Neugut 1998

Neugut AI, Jacobson JS, Suh S. The epidemiology of cancer of the small bowel. *Cancer Epidemiology Biomarkers Prevention* 1998;**7**:243-251.

O'Riordan 1996

O'Riordan BG, Vilor M, Herrera L. Small bowel tumors:an overview. *Digestive Diseases* 1996;**14**:245-257.

Okhusa 1991

Okhusa T, Ohtomo K, Yamamato N, Fujimoto H. Primary adenocarcinoma of duodenal bulb benefitted by chemotherapy. *Digestive Diseases and Sciences* 1991;**36**(11):1653-6.

Ouriel 1984

Ouriel K, Adams JT. Adenocarcinoma of the small intestine. *American Journal of Surgery* 1984;**147**:66-71.

Persson 1994

Persson PG, Karlen P, Bernell O, et al. Crohn's disease and cancer: A population based cohort study. *Gastroenterology* 1994;**107**:1675-1679.

Rose 1996

Rose DM, Hochwald SN, Klimstra DS, Brennan MF. Primary duodenal adenocarcinoma: a ten year experience with 79 patients. *Journal of the American College of Surgeons* 1996;**183**:89-96.

Sager 1978

SagerGF. Primary malignant tumors of the small intestine. *American Journal of Surgery* 1978;**135**:601.

William 1996

William M, Harnett PR. Adenocarcinoma of duodenum with liver metastases. Complete remission and long-term survival with 5-fluorouracil chemotherapy-a case report.. *American Journal of Clinical Oncology* 1996;**19**(3):305-6.

Williamson 1983

Williamson RC, Welch CE, Malt RA. Adenocarcinoma and lymphoma of small intestine. *Annals of Surgery* 1983;**197**:171.

Wilson 1974

Wilson JM, Melvin DB, et al. Primary malignancies of the small bowel. *Annals of Surgery* 1974;**180**:175-9.

Zhou 1997

Zhou Z, Wan D, Shi M. Diagnosis and treatment of primary malignant tumors of the small bowel. *Zhonghua Zhong Liu Za Zhi* 1997;**19**(4):297-9.

Zollinger 1986

Zollinger RM Jr. Primary neoplasms of the small intestine. *Amercian Journal of Surgery* 1986;**151**:654-8.

WHAT'S NEW

Date	Event	Description
10 April 2015	Review declared as stable	Editorial decision to park this review, due to lack of trials to support. None of the performed searches after publication have revealed any new trials. Authors have declared no further commitment to this title. If any new identified trial is found eligible for inclusion, an update will be considered with appointment of a new author team.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 3, 2007

Date	Event	Description
5 November 2009	New search has been performed	An updated search as on 1.11.2009 hasn't revealed any new studies. the conclusion remains unchanged.
14 July 2008	Amended	Converted to new review format.

Date	Event	Description
29 March 2007	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None Known

INDEX TERMS

Medical Subject Headings (MeSH)

*Intestine, Small; Adenocarcinoma [*drug therapy]; Chemotherapy, Adjuvant; Intestinal Neoplasms [*drug therapy]

MeSH check words

Humans