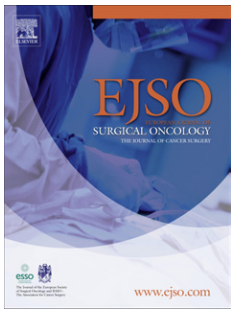
A phase I/II study of neoadjuvant chemotherapy with Pemetrexed (Alimta) in rectal cancer

K Derwinger, K Kodeda, T Swartling, P Kälebo, G Carlsson, B Gustavsson

Accepted Manuscript



Title: A phase I/II study of neoadjuvant chemotherapy with Pemetrexed (Alimta) in rectal cancer

Authors: K Derwinger, MD PhD K Kodeda, MD T Swartling, MD P Kälebo, MD PhD G Carlsson, MD PhD B Gustavsson, MD PhD

PII: S0748-7983(11)00249-6

DOI: 10.1016/j.ejso.2011.04.003

Reference: YEJSO 3148

To appear in: *European Journal of Surgical Oncology*

Accepted Date: 11 April 2011

Please cite this article as: Derwinger K, Kodeda K, Swartling T, Kälebo P, Carlsson G, Gustavsson B. A phase I/II study of neoadjuvant chemotherapy with Pemetrexed (Alimta) in rectal cancer, European Journal of Surgical Oncology (2011), doi: 10.1016/j.ejso.2011.04.003

A phase I/II study of neoadjuvant chemotherapy with Pemetrexed (Alimta) in rectal cancer

K Derwinger MD PhD [1], K Kodeda MD [1], T Swartling MD [1], P Kälebo MD PhD [2], G Carlsson MD PhD [1], B Gustavsson MD PhD [1]

Sahlgrenska Academy at
[1]Department of Surgery
[2]Department of Radiology
Sahlgrenska University Hospital/Östra
41685 Gothenburg, Sweden.
Corresponding author: Kristoffer Derwinger
Kristoffer.derwinger@vgregion.se

Number of figures: 2
Number of tables: 3

Running head: Preoperative Pemetrexed in rectal cancer

Keywords: Rectal Neoplasms
Neoadjuvant Therapy
Chemotherapy, Adjuvant
Pemetrexed
Alimta
Tumour size
MRI

Abstract

Aim
The aim was to assess the feasibility of preoperative chemotherapy and possible tumour response using Pemetrexed (Alimta) in rectal cancer.

Method
The study was a prospective, non-randomized, single centre phase I/II feasibility trial. 37 patients with resectable rectal cancer were recruited and given three 3 week cycles of preoperative Pemetrexed therapy. Tumour size and stage were assessed by MRI scans before and after chemotherapy. Treatment tolerability and response such as changes in tumour size and symptoms were assessed.

Results
All patients completed the chemotherapy. Whilst mild side effects were frequent (grade 1, 34/37), the risk of severe effects was limited (grade 3 or 4, 4/37). Overall, there was a significant reduction in tumour size ($p<0.001$). By RECIST criteria, one patient had tumour progression, 23/36 had stable disease and 12 patients had a response of up to 65%. There was also a significant decrease in the number of pretreatment symptoms ($p<0.018$) including reduction of bleeding and diarrhoea/constipation.

Conclusion
Preoperative (Neoadjuvant) treatment with Pemetrexed was feasible in studied patients. Serious side effects were limited and a radiological tumour response or stable disease was seen in a majority of patients.

Introduction

The best chance of cure for rectal cancer is achieved by a radical surgical procedure [1]. The oncological outcome after surgery has been improved with the introduction of TME (Total Mesorectal Excision). Surgery for rectal cancer is in general a major undertaking, especially in advanced cases, with considerable complication risks and high morbidity rates. Surgical outcomes have been further enhanced in when procedures are done in conjunction with adjuvant, and especially neoadjuvant radiotherapy [2, 3]. The chances of cure have improved along with a decreased risk of local recurrence. However, radiotherapy has some drawbacks and possible consequences of irradiating the pelvic area include impaired healing and bowel dysfunction. The collateral effect on the surrounding tissue can be significant and long lasting.

A rationale for using neoadjuvant chemotherapy is to provide early systemic cancer treatment with the aim of targeting possible circulating cancer cells, micro-metastasis and also potential tumour shrinkage. The therapy can be rapidly initiated without the delay and immunological stress caused by surgery. Today, neoadjuvant chemotherapy is mainly used together with long-term radiotherapy in the more advanced cases of rectal cancer in order to obtain down-sizing and down-staging, and thus enable curative surgery. However, there is an ongoing randomized study to evaluate possible benefits from neoadjuvant chemotherapy in colon cancer (the Foxtrot trial). Another line of development has been towards non-surgical treatment, which has led to some early promising results [4]. The reports of even complete responders, rendering surgery unnecessary or at least limiting the extent of the surgical procedure, could challenge the neoadjuvant strategies to further refinement. Limited surgical approach such as TEM (Transanal Endoscopic Microsurgery) can be an option for selected patients with small and early tumours which have favourable characteristics [5, 6]. Neoadjuvant treatment has then been used in this setting to improve local control [7].

The treatment cornerstone in gastrointestinal cancer is 5-fluorouracil (5-FU), a direct inhibitor of thymidylate synthase (TS) which is a key enzyme in the folate metabolism and thus indirectly involved in DNA synthesis [8]. Drugs with other pharmacodynamic mechanisms such as Irinotecan and Oxaliplatin have been developed and added into combination regimes, resulting in better outcome, but at the price of more side effects. Efforts have been made to replace 5-FU by developing new TS inhibitors which aim to achieve better effect with less side effects and a to produce a drug easier and less resource-intensive to administer. The initial development of so-called new multi-target antifolates has been hampered by severe side-effects. These effects have been reduced by the paradox of supplementing folates [9, 10] which permits the use of other TS inhibitors, like Pemetrexed, with an acceptable risk for the patient without know reduction of treatment effect [11, 12]. The role of Pemetrexed (Alimta) in the neoadjuvant treatment of rectal cancer is unknown. The aim of the study was to assess the feasibility of Pemetrexed in neoadjuvant treatment of rectal cancer. A secondary aim was to assess the possible tumour response.

Materials and methods

Patient and method

The study was a single centre, prospective, non-randomized and single-armed phase I/II feasibility trial. The inclusion and exclusion criteria were as presented in figure 1. The study was approved by the regional ethical review board. A total of 37 patients were recruited between June 1st, 2006 and January 30th, 2008. In the same institution, 87 patients were

operated on for rectal cancer during the same time period but were either ineligible, not asked to participate or declined participation. Characteristics of these 87 patients were also retrieved and they constitute a reference to the study group. The pre-treatment radiological investigation consisted of chest x-ray and MRI scan of the liver and the pelvis. A secondary MRI scan of the liver and pelvis was done after the three treatment cycles and thus before surgery. The study algorithm is summarized in figure 2.

Radiology

MRI was performed on a 1.5 T scanner (Philips Intera), using a body synergy coil for abdominal scans and a synergy cardiac coil for pelvic examinations. The MRI scans were performed as a combined protocol, starting with upper abdomen (liver) and then pelvis. Prior to scanning, spasmolytics were given, Buscopan 20 + 20 mg i.v. and Glucagon 1 mg i.m. Upper abdominal scans included axial respiratory triggered T2-weighted TSE images with 5 mm slice thickness, axial breathhold T1-weighted in-and-out of phase gradient echo images with 5 mm slice thickness and an axial breathold 3D T1-weighted gradient echo imaging with fatsaturation (Thrive, Philips) after i.v. Gadolinium enhancement in venous phase with 2 mm slice thickness. Pelvic imaging included axial Thrive imaging and T2-weighted TSE images with 3 mm slice thickness in sagital, oblique axial and oblique coronal plane, with an in plane resolution of 0.6-0.7 mm. Staging was performed on the pelvic T2-weighted images and a quantitative value of tumour size was expressed and measured as maximal tumour area in mm^2 on the oblique axial T2-weighted images. All readings and measurements were performed by one expert radiologist.

Assessment

Any preoperative radiotherapy was given as indicated and planned in a preoperative multidisciplinary team conference and by regular guidelines. Neither radiotherapy nor the surgical plan was changed due to the study. The charts including the pathology reports were reviewed for relevant data, including treatment tolerability and possible side effects. Side effects were scored according to NCI criteria and standards [13]. The pre- and post-treatment radiological evaluations were assessed including measurement of the maximal tumour area before and after treatment. The outcome was compared to the RECIST effect criteria [14]. The data were assessed by degree of treatment response, side effects and also related to pathology data. Finally the data were compared with those of the reference group, including survival and tumour recurrence.

Chemotherapy

The treatment started with vitamin supplementation to reduce the risk and degree of possible side-effects. Patients were given a vitamin B12 (1 mg) intramuscular injection at least 1 week prior to the first treatment and repeated every 9 weeks until 3 weeks after the final treatment. In addition a daily oral multivitamin supplementation containing 0.80 mg folic acid was started at least 5 days prior to the first treatment and discontinued 3 weeks after the final treatment. The chemotherapy was given on three occasions with 3-week intervals. Pemetrexed (500 mg/m^2) was infused over 10 minutes (8-15 minutes). Dexamethasone 4 mg was given p.o. twice daily the day before treatment, on the day of treatment and one day after the Pemetrexed infusion. The use of antiemetic drugs and regular medications apart from ASA/NSAID was not affected by the study protocol.

Statistics

The JMP 8.0 statistics software (SAS Inc) was used for the analyses. Statistical analyses performed included chi-square (χ^2), independent-samples t-test, ANOVA and paired-samples

t-test as indicated. Findings with two-sided p-values <0.05 were considered statistically significant.

Results

Patients and symptoms

The patient characteristics are summarized in table 1. The Pemetrexed group with a median age of 61 years was significantly younger (t-test, p=0.002) and had a higher proportion of males than the reference group. There was no statistically significant difference in T or N-stage, differentiation grade or overall stage (χ^2). The pathology including node assessment was equal and meeting international staging criteria, with a median of 17 nodes assessed. 26/37 patients received short-term (5x5 Gray) and 2/37 patients long-term (25x2 Gray) preoperative radiotherapy. Early cancers (T2) were the main reason for omitting preoperative radiotherapy. The pre-treatment symptoms included rectal bleeding, 29/37 patients, and diarrhoea/constipation in 20/37 patients.

Treatment response and tolerability

All patients completed the chemotherapy program. The MRI scans of one patient were impossible to evaluate due to motion artefacts. 36 patients had assessable MRI series. Five patients had some degree of size increase and 31 patients had a tumour size reduction. When referenced to RECIST criteria one patient had progression of tumour size whilst 12 had a partial response and 23 had stable disease, as summarized in table 3. The overall tumour size decreased from 663 to 539 mm^2 (paired-samples t-test, p<0.0001). There was no statistical relation between the treatment response and the tumours T-/ N-stage, patient age or tumour location level (chi-square/ANOVA). The tumours of poor differentiation grade (G3) were larger than the median size and had a larger size reduction in mm^2 but not proportionally in percentage. The side effects during the Pemetrexed treatment were as summarized in table 2. Three patients had no side effects. Most side effects were grade 1 except neutropenia suffered by 11 patients of whom 4 developed grade 3 or 4 side effects. Another exception was 4 patients with grade 2 fatigue. No patients terminated the treatment pre-emptively and none required hospitalization due to the side effects. There was no relation between the tumour response and the degree of side effects (χ^2). There was a statistically significant decrease in number of pre-treatment symptoms (χ^2, p=0.018). The symptoms most affected was those of bleeding (post-treatment 9/37, χ^2, p=0.024) and diarrhoea/constipation (post-treatment 9/37, χ^2, p=0.015). The effect of symptom relief came, in most instances, early and within the first two treatment cycles.

Outcome

The median length of hospital stay was 10 days in both groups. All study patients were discharged home and there was no (30 days) postoperative mortality in the study group. 11 study patients, mainly with stage III-disease, received postoperative adjuvant chemotherapy based on 5-FU and Oxaliplatin compared with 17 patients in the reference group. The corresponding figures for first line treatment after disease recurrence were 5 and 8 patients respectively. The median follow-up time was 29 months. During follow-up there have been 5 recurrences in the Pemetrexed group. The risk of recurrence was significantly associated with poor tumour differentiation grade (χ^2, p=0.005) and a high N-status (χ^2, p=0.040). There was no statistical association between the recurrence and preoperative treatment effect or decrease in tumour size. Three patients including one with stage IV disease have died due to disease

progression. There has also been one non-cancer related death. There was no significant difference (χ^2) in the frequency of postoperative events when compared to the reference group.

Discussion

Key findings

A rationale of neoadjuvant chemotherapy is the early systemic cancer treatment which also could target possible metastasis and circulating cancer cells. The therapy can be initiated rapidly and thus is unaffected by the delay caused by surgery and the time needed for postoperative recovery and healing. Other issues of possible importance are the immunological stress and inflammatory responses triggered by surgery along with the stimulation of cell proliferation needed for wound healing [15, 16]. Little is known how the surgical trauma affects the risk of distant metastases and if this could be modulated by preoperative chemotherapy [17, 18]. In the present study a neoadjuvant treatment with Pemetrexed (Alimta), a more recent TS inhibitor, was assessed for feasibility in rectal cancer. Pemetrexed has a wider target mechanism than 5-FU and has shown activity against mesothelioma [19], non-small-cell lung cancer [20] and also been tested in advanced colorectal cancer [21]. Pemetrexed is resource-effective with only one hospital visit every 21 days, without need for hospitalization. Most alternatives are more resource intensive with an exception of the oral 5-FU prodrug capecitabin [22]. An important attribute of Pemetrexed is the possibility to control and reduce many of its associated clinical toxicities without affecting efficacy [9]. The incidence of serious side effects in the study was limited and a radiological tumour response or stable disease was seen in a majority of patients. A preoperative tumour downsizing could hypothetically facilitate certain technical aspects of the surgical procedure and for instance possibly permit a larger proportion of laparoscopic procedures.

Tolerability

The risk of side effects in both frequency and their severity has been and still is an issue of concern in the development and use of cytotoxic drugs. 5-FU has been one of the main cytotoxic agents used in colorectal cancer for more than 40 years. Efforts have been made to find newer and more efficient TS inhibitors [8]. However, the early positive findings were counter-balanced by severe toxicity and even mortality. The finding that a supplementation of folic acid and vitamin B12 could decrease the severity of the side effects was important and enabled the continued use of this agent [10]. The findings were in line with those of our study where side effects were frequent (92% of the patients), but mild and thus at a level acceptable for the patients (table 2). The risk of higher grade toxicities was substantially lower. As a comparison Petrelli et al reported diarrhoea in 40% of the patients with 26% needing hospitalization for rehydration [23]. The 4/37 patients with a grade 3/4 neutropenia was less than the 17 % reported by Louvet et al in advanced colorectal cancer [24]. The risks could also be compared to the 41% grade 3+ neutropenia along with a 10.8% risk of grade 3/4 diarrhoea reported for FOLFOX regimes [25]. The overall treatment tolerability in this study could be considered as good as all patients were able to complete the planned chemotherapy and none required hospital care due to side effects.

Tumour effect

A neoadjuvant study provides a visible target lesion evaluable by repeated radiological examinations. The comparable study setting would be in advanced disease with known metastasis. Louvet et al studied Pemetrexed based regimes in metastatic colorectal cancer and reported 23% response rate along with 50% stable disease. Our findings are comparable in efficacy with a 33% response rate against RECIST criteria and up to 64% stable disease (table 3). The response could also be measured against the 33% response rate reported by Shin et al for FOLFOX/FIRI treatment in stage IV colorectal cancer [26]. Another measure of treatment effect was the substantial reduction of tumour associated symptoms. Several patients experienced a reduction of pre-treatment symptoms and foremost those of bleeding and bowel-function disturbances. The early effect of symptom relief within the first two treatment cycles is interesting. A plausible explanation could be due to the reduction of local inflammation and oedema. The visible treatment response could provide information of prognostic interest and has been associated with improved survival in advanced disease [14]. The effect or lack thereof can also be of importance in relation to the choice of regime, such as in the case of complimentary adjuvant treatment for stage III disease with lymph node metastasis.

Strength and weakness

The study was a phase I/II feasibility trial on neoadjuvant chemotherapy in rectal cancer. Thus, there are the associated weaknesses of the limited number of assessed patients and that there was no randomization of controls. As a single-centre study all patients were treated along the same guidelines and the same staff performed all treatment, assessments and registrations. The optimal way of assessing the tumour size of a rectal cancer is not known but the maximum area is one possibility. The assessments of MRI scans were done by the same radiologist and thus in a consequent manner improving the internal validity for assessing changes in size. The pathology assessment fully met the international UICC standards and thus providing a valid cancer staging. The time from diagnosis to the initiation of treatment was considerably shorter in the treatment group than what we are usually capable to achieve in our institution in terms of time from diagnosis to surgery. The rapid therapy start did possibly benefit study accrual. In our opinion, the difference in age and stage between the study population and the reference group, doesn't change the feasibility results but could have impact on long-term outcome assessments. The absence of outcome difference compared to the reference group is difficult to assess as the groups are small and the follow-up time limited.

Conclusion

Preoperative (Neoadjuvant) treatment with Pemetrexed was feasible in all studied patients. Serious side effects were limited and a radiological tumour response or stable disease was seen in a majority of patients. The results should be confirmed in larger studies focusing on efficacy and safety.

Acknowledgements

We thank The Swedish Cancer Society, the Gothenburg University, the Gothenburg Medical Association, the Björnsson Foundation and the Lundberg Foundation for financial support.

We would also like to express our gratitude to Hillevi Björkqvist for assisting in the collection and registration of data and samples and to Dr Cormac Owens for linguistic support.

Conflict of interest

The study was performed with financial support from Eli-Lilly. The authors did not receive any individual financial support and Eli-Lilly had no influence on collection or interpretation of here presented data. The authors declare no conflicts of interest.

References

1. Kusunoki, M. and Y. Inoue, *Current surgical management of rectal cancer.* Dig Surg, 2007. **24**(2): p. 115-9.
2. Moser, L., J.P. Ritz, W. Hinkelbein, et al., *Adjuvant and neoadjuvant chemoradiation or radiotherapy in rectal cancer--a review focusing on open questions.* Int J Colorectal Dis, 2008. **23**(3): p. 227-36.
3. Bauer, T.W. and F.R. Spitz, *Adjuvant and neoadjuvant chemoradiation therapy for primary colorectal cancer.* Surg Oncol, 1998. **7**(3-4): p. 175-81.
4. Habr-Gama, A., R.O. Perez, J. Sabbaga, et al., *Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period.* Dis Colon Rectum, 2009. **52**(12): p. 1927-34.
5. De Graaf, E.J., P.G. Doornebosch, R.A. Tollenaar, et al., *Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention.* Eur J Surg Oncol, 2009. **35**(12): p. 1280-5.
6. Dias, A.R., C.S. Nahas, C.F. Marques, et al., *Transanal endoscopic microsurgery: indications, results and controversies.* Tech Coloproctol, 2009. **13**(2): p. 105-11.
7. Lezoche, G., M. Baldarelli, M. Guerrieri, et al., *A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy.* Surg Endosc, 2008. **22**(2): p. 352-8.
8. Danenberg, P.V., H. Malli and S. Swenson, *Thymidylate synthase inhibitors.* Semin Oncol, 1999. **26**(6): p. 621-31.
9. Calvert, A.H., *Biochemical pharmacology of pemetrexed.* Oncology (Williston Park), 2004. **18**(13 Suppl 8): p. 13-7.
10. Calvert, H., *Folate status and the safety profile of antifolates.* Semin Oncol, 2002. **29**(2 Suppl 5): p. 3-7.
11. Kut, V., J.D. Patel and A. Argiris, *Pemetrexed: a novel antifolate agent enters clinical practice.* Expert Rev Anticancer Ther, 2004. **4**(4): p. 511-22.
12. Rollins, K.D. and C. Lindley, *Pemetrexed: a multitargeted antifolate.* Clin Ther, 2005. **27**(9): p. 1343-82.
13. NCI, N.C.I.-. *CTC - Common Toxicity Criteria, 2.0.* 1999.
14. Eisenhauer, E.A., P. Therasse, J. Bogaerts, et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.
15. Fahmy, R.G., C.R. Dass, L.Q. Sun, et al., *Transcription factor Egr-1 supports FGF-dependent angiogenesis during neovascularization and tumor growth.* Nat Med, 2003. **9**(8): p. 1026-32.
16. Finlay, I.G., D. Meek, F. Brunton, et al., *Growth rate of hepatic metastases in colorectal carcinoma.* Br J Surg, 1988. **75**(7): p. 641-4.
17. Miki, C., K. Tanaka, Y. Inoue, et al., *Perioperative host-tumor inflammatory interactions: a potential trigger for disease recurrence following a curative resection for colorectal cancer.* Surg Today, 2008. **38**(7): p. 579-84.
18. van der Bij, G.J., S.J. Oosterling, R.H. Beelen, et al., *The perioperative period is an underutilized window of therapeutic opportunity in patients with colorectal cancer.* Ann Surg, 2009. **249**(5): p. 727-34.
19. Jackman, D.M., *Current options for systemic therapy in mesothelioma.* Semin Thorac Cardiovasc Surg, 2009. **21**(2): p. 154-8.

20. Manegold, C., G. Schmid-Bindert and L.R. Pilz, *Pemetrexed for the treatment of non-small-cell lung cancer.* Expert Rev Anticancer Ther, 2009. **9**(9): p. 1195-209.
21. Atkins, J.N., S.A. Jacobs, H.S. Wieand, et al., *Pemetrexed/oxaliplatin for first-line treatment of patients with advanced colorectal cancer: a phase II trial of the National Surgical Adjuvant Breast and Bowel Project Foundation Research Program.* Clin Colorectal Cancer, 2005. **5**(3): p. 181-7.
22. Folprecht, G. and C.H. Kohne, *Drug Insight: Metastatic colorectal cancer--oral fluoropyrimidines and new perspectives in the adjuvant setting.* Nat Clin Pract Oncol, 2005. **2**(11): p. 578-87.
23. Petrelli, N., L. Herrera, Y. Rustum, et al., *A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma.* J Clin Oncol, 1987. **5**(10): p. 1559-65.
24. Louvet, C. and A. de Gramont, *Pemetrexed in advanced colorectal cancer.* Oncology (Williston Park), 2004. **18**(13 Suppl 8): p. 56-62.
25. Sharif, S., M.J. O'Connell, G. Yothers, et al., *FOLFOX and FLOX regimens for the adjuvant treatment of resected stage II and III colon cancer.* Cancer Invest, 2008. **26**(9): p. 956-63.
26. Shin, S.J., J.B. Ahn, H.J. Choi, et al., *The combination of capecitabine and irinotecan in treating 5-Fluorouracil- and Oxaliplatin-pretreated metastatic colorectal cancer.* Cancer Chemother Pharmacol, 2008. **61**(1): p. 75-81.

Concerning the manuscript:

Neoadjuvant chemotherapy with Pemetrexed (Alimta) in rectal cancer

The study was performed with financial support from Eli-Lilly.
However, the authors did not receive any individual financial support and Eli-Lilly had no influence on collection or interpretation of here presented data. The authors declare no conflicts of interest.

Kristoffer Derwinger MD PhD, Karl Kodeda MD , Torbjörn Swartling MD , Peter Kälebo MD PhD , Göran Carlsson MD PhD , Bengt Gustavsson MD PhD

Corresponding author: Kristoffer Derwinger
Kristoffer.derwinger@vgregion.se
Sahlgrenska Academy at
Sahlgrenska University Hospital/Östra
41685 Gothenburg, Sweden.

	Alimta group (n=37)	Reference group (n=87)
Age (median (i.q. range))	61 (56-66)	68 (59-78)
Gender (male/female)	26/11	39/48
Operation (AR/APR/Hartman)	25/11/1	49/28/14
Laparoscopy (yes/no)	9/28	20/67
Overall stage (I/II/III/IV)	7/15/13/2	10/29/39/9
Differentiation grade (G1/2/3/4)	1/29/2/5	1/73/6/7
T-stage (T1-4)	3/9/22/3	3/25/48/11
N-stage (N0-2)	22/10/5	41/28/18
Assessed nodes (median(i.q. range))	17 (14-22)	20 (15-25)

Table 1. Demographics and pathology data of the patient in the Alimta study (n=37) and the patients treated for rectal cancer during the same period (n=87).

Side-effect	Toxicity grading (NCI)			Total
	1	2	3/4	
Fatigue	21	4	0	25
Eye-related	17	0	0	17
Skin-related	13	0	0	13
Neutropenia	2	5	4	11
Nausea	17	0	0	17
Bowel-related	6	1	0	7

Table 2. Side-effects and their grade (according to NCI criteria) during Alimta treatment (n=37).

Preoperative treatment effect	N	Definition (RECIST)	Pretreatment tumour size (MRI 1)	Post treatment size (MRI 2)	Decrease mm^2	Decrease %
Progressive disease	1	>20 % increase	505	621	-116	-23
Stable disease	23	<30% decrease	688 (233-1345)	610 (231-1431)	37 (-86-237)	9 (-16-29)
Partial response	12	≥30% decrease	512 (296-1203)	344 (150-618)	201 (125-607)	43 (30-65)
Total	36	All	603 (233-1345)	514 (150-1431)	114 (-116-607)	15 (-23-65)

Table 3. Treatment and response in the Alimta group (n=36). The values represent the maximum axial tumour area in mm^2 (median (range)) as assessed by pre and post-treatment MRI.

Inclusion criteria

Resectable rectal cancer (<15 cm from the anal verge)
Biopsy-verified adenocarcinoma
Age > 18 years
Good general condition (WHO performance status of 0 or 1)
Normal hepatic, renal and bone-marrow function
Reliable method of contraception
Life expectancy >12 weeks.

Exclusion criteria

Previous treatment of rectal cancer
Other synchroneous malignancy or concomitant oncological treatment
Pregnancy or breastfeeding
A history of neurological or psychiatric disorders (including dementia)
Site of residence making adequate follow-up unfeasible
Inability or unwillingness to receive any of the used medications or inability to discontinue ASA/NSAID-treatment 2 days before and after administration of Pemetrexed.

Figure 1. The inclusion and exclusion criteria of the study.

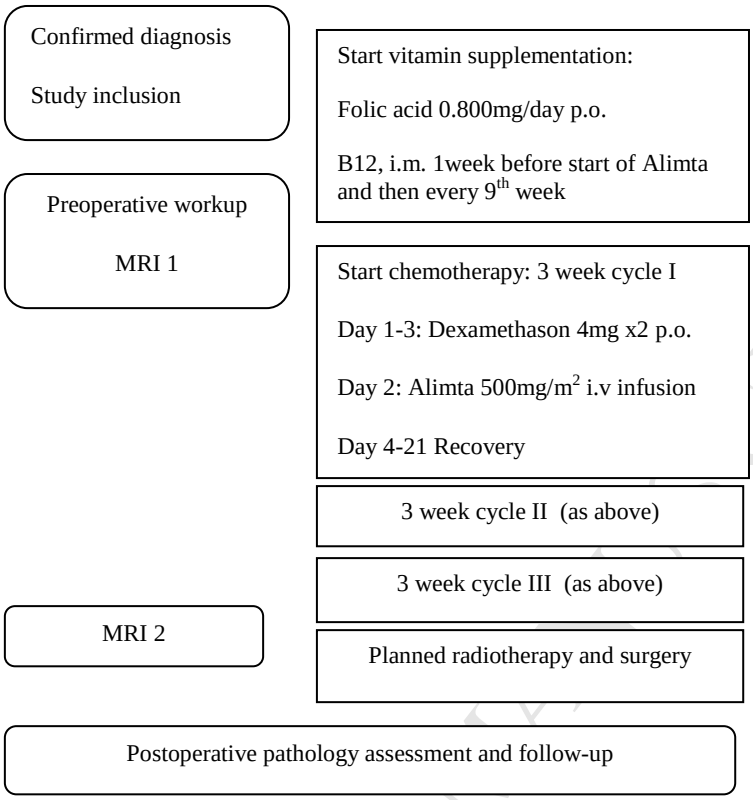


Figure 2. The study algorithm of treatment and examinations.