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V. Velenik, J. Ocvirk, I. Oblak, F. Anderluh. A phase II study of cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with locally advanced resectable rectal cancer. *EJSO - European Journal of Surgical Oncology*, WB Saunders, 2010, 36 (3), pp.244. 10.1016/j.ejso.2009.12.002 . hal-00566751

HAL Id: hal-00566751

<https://hal.archives-ouvertes.fr/hal-00566751>

Submitted on 17 Feb 2011

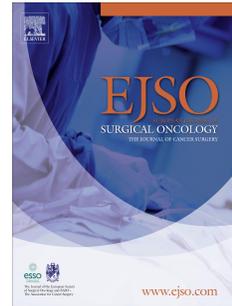
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Accepted Manuscript

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PII: S0748-7983(09)00543-5

DOI: [10.1016/j.ejso.2009.12.002](https://doi.org/10.1016/j.ejso.2009.12.002)

Reference: YEJSO 2925

To appear in: *European Journal of Surgical Oncology*

Received Date: 23 May 2009

Revised Date: 29 November 2009

Accepted Date: 7 December 2009

Please cite this article as: Velenik V, Ocvirk J, Oblak I, Anderluh F. A phase II study of cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with locally advanced resectable rectal cancer, *European Journal of Surgical Oncology* (2009), doi: 10.1016/j.ejso.2009.12.002

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A phase II study of cetuximab, capecitabine and radiotherapy in neoadjuvant treatment of patients with locally advanced resectable rectal cancer

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Abstract**Background**

Neoadjuvant chemoradiotherapy (CRT) reduces local tumor recurrence in locally advanced rectal cancer (LARC). This phase II study assessed neoadjuvant cetuximab with capecitabine-based CRT in LARC.

Methods

Patients with stage II/III LARC received capecitabine 1250 mg/m² twice daily for 2 weeks followed by intravenous cetuximab 400 mg/m² at week 3, then weekly intravenous 250 mg/m² cetuximab plus CRT including capecitabine 825 mg/m² twice daily (including weekends during radiotherapy) with radiotherapy of 45 Gy (25 x 1.8 Gy), 5 days a week for 5 weeks. Total mesorectal excision was scheduled 4–6 weeks following completion of CRT. The primary endpoint was pathological complete response (pCR).

Results

Thirty-seven patients were eligible for safety and efficacy. TMN staging at baseline was: T4N2, 11%; T3N2, 40%; T2N2, 3%; T3N1, 35%; T2N1, 3% and T3N0 8%. The most common adverse events included, grade 1/2 acneiform skin rash (86%), and grade 3 radiodermatitis, (16%), diarrhea (11%) and hypersensitivity (5%). pCR was achieved in 3 patients (8%). Overall, T- and N-downstaging rates were 73%, 57% and 81% respectively. Total sphincter preservation rate was 76%, and 53% in 17 patients whose tumors were located within 5 cm from the anal verge. Non-fatal perioperative complications occurred in 13 patients (35%) with delayed wound healing occurring in 6 patients (16%). One death was recorded due to sepsis following colonic necrosis.

Conclusion

Neoadjuvant cetuximab with capecitabine-based CRT is tolerable in patients with resectable LARC. Whilst the pCR rate was similar to recent reports, a high pathological downstaging rate was achieved.

Key words: rectal cancer, neoadjuvant chemoradiotherapy, capecitabine, cetuximab

Introduction

Multimodal treatment strategies aim to reduce tumor recurrence rates and improve survival in patients with resectable locally advanced rectal cancer (LARC). Pre- and postoperative radiotherapy are reported to decrease the risk of local relapse in this setting.¹⁻³ Chemotherapy in combination with radiotherapy can act as a radiosensitizing agent, potentially eradicating micrometastases. The combination of postoperative 5-fluorouracil (5-FU)-based chemotherapy with radiation in the treatment of LARC is reported to improve patient disease-free survival (DFS) and overall survival.⁴ Lower rates of local regional failure (13% vs. 6%) in patients receiving preoperative 5-FU-based chemoradiotherapy (CRT) compared with postoperative 5-FU-based CRT have also been demonstrated.⁵ The addition of continuous infusion (CI) 5-FU-based chemotherapy concurrently to preoperative long-term fractionation radiation is now considered by many to be the standard of care for LARC patients in Europe, following data from prospective randomized studies.^{6,7} However, whilst rates of pathological complete response (pCR) and local control were found to be higher in the CRT arms than radiotherapy alone arms, no significant improvements to DFS or overall survival were found, with the occurrence of metastatic disease remaining a problem.⁶⁻⁸ Thus new combinations of chemotherapeutic agents for CRT in LARC patients are urgently sought.

Capecitabine (Xeloda, Hoffmann-La Roche Ltd, Basel Switzerland) an oral fluoropyrimidine prodrug is readily absorbed into the gastrointestinal tract and activated primarily in tumor cells displaying high levels of thymidine phosphorylase.⁹ Capecitabine has the same efficacy as CI 5-FU but with less of the associated toxic side effects,^{9,10} and has demonstrated radiosensitizing properties *in vivo*.¹¹ Furthermore when capecitabine was administered concomitantly with radiotherapy to LARC patients in phase II studies, low toxicity profiles, tumor downstaging and pCR rates ranging from 4-31% were reported.^{12,13}

Cetuximab (Erbix developed by Merck KGaA Darmstadt, Germany [under license from Imclone, NY, USA]) an immunoglobulin G1 monoclonal antibody specifically targets the epidermal growth factor receptor (EGFR), competitively inhibiting ligand binding and ligand-dependent downstream signaling.^{14,15} Cetuximab in combination with chemotherapy has demonstrated improved efficacy in the first-line treatment of patients with EGFR expressing metastatic CRC (mCRC) compared with chemotherapy alone arms.^{16,17} Furthermore cetuximab has been shown to be safely administered with radiotherapy, improving survival in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).¹⁸

EGFR expression has been associated with reduced DFS in patients with LARC following preoperative CRT.^{19,20} Thus EGFR-targeted agents appear to be attractive candidates for use with CRT in this setting. Recent phase I/II studies have reported acceptable toxicity and tumor downstaging when cetuximab was administered in combination with fluoropyrimidine-based CRT in rectal cancer patients.^{21,22} In the present study the addition of cetuximab to capecitabine-based CRT was investigated in the neoadjuvant treatment of resectable LARC patients.

Patients and Methods

Study design

This was a prospective, open-label single center phase II study. The protocol was approved by the Ethical Committee of Slovenia, Agency for Medicinal Products and Medical Devices, Ministry of Health and by the Independent Ethical Committee of the Institute of Oncology, Ljubljana, Slovenia. The trial was registered at ClinicalTrials.gov. (NCT00689702). The study was conducted in accordance with the principles of the Declaration of Helsinki and the note for guidance on good clinical practice.

Main eligibility criteria

Eligible patients had a histologically verified stage II or III adenocarcinoma of the rectum, (International Union against Cancer [UICC] TNM classification 2002). Other inclusion criteria were; ≥ 18 years of age at diagnosis; World Health Organization (WHO) performance status ≤ 2 ; adequate bone marrow, liver, renal and cardiac function (no history of ischemic heart disease); no prior radiotherapy and/or chemotherapy; signed informed consent. Exclusion criteria included; patients with a history of prior malignancy other than non-melanoma skin cancer or in situ carcinoma of the cervix; a known hypersensitivity to biological agents; pregnant or lactating patients.

Pretreatment evaluation

Patient pretreatment work-up comprised a complete history, physical examination, full blood count, serum biochemistry, carcinoembryonic antigen, chest radiography, ultrasonography (US) and/or a computed tomography (CT) scan of the whole abdomen and colonoscopy with biopsy. The extent of locoregional disease was determined by magnetic resonance imaging (MRI) of the pelvis (100%); 56% of patients also had endoscopic US and 7% had a CT scan of the pelvis.

Patient treatment

A summary of the study treatment is shown in Figure 1. Patients received capecitabine 1250 mg/m² twice daily for 2 weeks. Cetuximab 400 mg/m² was intravenously administered on week 3, followed by 250 mg/m²/week during radiotherapy. Radiotherapy started on week 4 and was delivered once a day using 15 MV photon beams and a four-field box technique, 5 days a week. The small pelvis received 45 Gy in 25 fractions of 1.8 Gy over 5 weeks. Three-dimensional conformal CT-based treatment planning was performed. The clinical target volume (CTV) encompassed the primary tumor, entire mesorectal tissue, and internal iliac and presacral lymph nodes up to the L5/S1 junction and 5 cm distal to the primary tumor. An additional 1 cm in all directions was added to the CTV to obtain the planning target volume (PTV). During irradiation, patients were treated in the prone position, with a full bladder, and a belly-board immobilization device was used. A multileaf collimator was used for shaping the fields and for the protection of normal tissues. Chemotherapy was administered concomitantly with radiotherapy and consisted of capecitabine administered orally at a daily dose of 1650 mg/m², divided into two equal doses given 12 hours apart, one administered an hour prior to irradiation. Chemotherapy was started on the first day and finished on the last day of radiotherapy (including weekends).

Patient and tumor assessments

During treatment, patients were evaluated weekly. Clinical examinations and complete blood counts were performed and body weight was measured. Toxic side effects were assessed according to National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0).

Following re-evaluation of the primary tumor with pelvic MRI and an assessment of tumor response as defined by RECIST criteria, definitive surgery was scheduled for 6 weeks after the completion of CRT. Surgical management included a sphincter preservation approach whenever possible, using the total mesorectal excision (TME) technique. The option for a temporary colostomy during surgery was left to the surgeon's discretion.

Postoperative, pathological evaluation of the surgical specimen was performed. Pathological complete response was defined as the complete disappearance of all tumor cells. Histological regression of the primary tumor was semi-quantitatively determined according to a 5 scale tumor regression grading (TRG)²³: TRG 0, no regression; TRG 1, minimal regression (dominant tumor mass with obvious fibrosis and/or vasculopathy); TRG 2, moderate regression (predominantly fibrotic changes with few tumor cells or groups); TRG 3,

good regression (very few tumor cells in fibrotic tissue); TRG 4, total regression (no tumor cells, only fibrotic mass).

Postoperative chemotherapy

Postoperative adjuvant treatment with capecitabine for 3 cycles starting within 6 weeks after surgery was recommended. A three-week cycle consisted of 2 weeks of capecitabine treatment (1250 mg/m² twice-daily) followed by a 1 week treatment break.

Statistical considerations

The primary endpoint of the study was the pCR rate. At the time of the study design the reported pCR for neoadjuvant capecitabine-based CRT in LARC ranged from 4–31%, including 9% from our previously reported phase II trial.¹³ The aim was to evaluate whether a 26% pCR rate was achievable by adding cetuximab to standard preoperative treatment. The lowest pCR rate of interest was set at 10%, with an alpha error of 5% and a power of 80%, a minimum of 29 evaluable patients were needed (calculated using power sample calculation, for single sample percentages $\alpha=5\%$, $1-\beta=20\%$). Assuming that 10% or more patients would not be evaluable the aim was to enroll at least 35 patients.

Secondary endpoints included: the sphincter preservation rate (SPR) in low-sited tumors, overall tumor downstaging rate, the rate of radical (R0) resections and toxicity. The effect of preoperative CRT on tumor downstaging was assessed by comparing the pretreatment radiologically determined TNM stage with the postoperative pathologic TNM stage. Statistics were descriptive and analyzed using the SPSS statistical software package, version 13, (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Forty-three patients with resectable primary LARC were recruited between February 2007 and September 2008. One patient did not receive study treatment due to the detection of metastatic disease during the pretreatment work-up. One patient withdrew consent following three weeks of treatment, and another was excluded due to protocol violation. One patient was discontinued from chemotherapy on day 4 of treatment following the development of cardiac ischemia demonstrated on electrocardiogram (ECG), and was subsequently treated with radiation (50.4 Gy) only. Two patients were withdrawn from capecitabine treatment after 4 and 6 days due to chest pain of unknown origin, these patients were treated with

radiotherapy (50.4 Gy) and with two 5-day cycles of 5-FU (425 mg/m²/day) and leucovorin (20 mg/m²/day) in protracted infusion but did not receive cetuximab. Thus 37 patients received cetuximab and completed the preoperative treatment protocol and comprised the safety population who were also evaluable for efficacy. Patient and disease characteristics are summarized in Table 1. The most frequent MRI staging was uT3N+ (75%). In 18 patients the primary tumor was sited 5 cm or less from the anal verge.

Acute toxicity and treatment compliance

Neoadjuvant treatment with cetuximab was discontinued after the first administration in 4/37 patients due to hypersensitivity reactions. These patients were subsequently treated with capecitabine and radiation only. For one patient 2 doses of cetuximab were omitted due to grade 3 hepatotoxicity. All patients received the planned dose of radiation. The median duration for radiotherapy treatment was 33 days (range 33–43 days). The median time of interruption to radiotherapy treatment was 2 days (range 1–7 days) and occurred in 30 patients, due to treatment-related toxicity (4 patients) or mechanical failure/ holiday period (26 patients). The median duration of chemotherapy with capecitabine during radiotherapy was 33 days (range 33–43 days) and the median time of chemotherapy interruption was 6 days (range 1–11 days). Only two patients received less than 90% of the planned capecitabine dose due to grade 3 hepatotoxicity, (one patient) and grade 3 diarrhea, (one patient). The relative dose intensity for cetuximab, capecitabine and radiotherapy was 91%, 98% and 100% respectively.

The frequency and grade of treatment-related acute toxicities are summarized in Table 2. The most frequent side-effect of CRT was grade 1/2 acneiform rash. The most frequent grade 3 adverse event was radiodermatitis. During the treatment period, 22 patients lost weight compared with the beginning of treatment. The maximum body weight loss was 19% (median 5%). Of the remaining patients, eight succeeded in maintaining a constant weight, and nine patients experienced a weight increase of up to 6% (median 1%).

Surgery and perioperative toxicity

A summary of patient surgery and perioperative toxicity is shown in Table 3. All patients underwent definitive surgery following neoadjuvant therapy and were operated on between 31 and 59 days (median 41 days) after the last day of CRT. The median hospital stay for surgery was 10 days (range; 7–32 days), and the most common operation was low anterior resection. A temporary stoma was created in 22/28 patients undergoing sphincter preservation surgery. As determined by histopathological examination of surgical specimens,

resection with negative circumferential margins at the primary tumor site was achieved in all patients. For one patient undergoing a low anterior resection, microscopic foci of cancer cells were found in the distal surgical margin (R1 resection) and this patient subsequently underwent an abdominoperineal resection, with no tumor cells detected on histopathological inspection of the resected tissue.

No perioperative deaths were recorded within one month following surgery. Non-lethal perioperative complications were recorded in 13 patients, with the most common cause due to wound healing problems (Table 3). Two patients required further operations (one patient for anastomotic leakage and abdominal abscess, and one patient for an incarcerated transversostoma).

Efficacy

Pathological TNM stages, as assessed on histopathological examination of resected specimens, in relation to preoperative TNM status, are presented in Table 4. Three patients demonstrated pCR (TRG4; 8.1%, 95% CI -8.8 to 8.8%). TRG 3, 2 and 1 were found in seven (19%), 19 (51%), and seven patients (19%) respectively. Overall downstaging occurred in 27/37 patients (73%) with decreases in T- and N-stages observed in 21 (57%) and 30 patients (81%), respectively. Increases in T- and/or N-stages (upstaging) were not recorded.

Tumor response as defined by RECIST on MRI imaging was evaluated in 34/37 patients by independent surgeons and radiologists blinded to patient clinical data. In three patients the control MRI before surgery was not performed (due to mechanical failure for two patients and for unknown reasons for one patient). Objective complete response (CR) was observed in four patients, partial response (PR) in 20 patients, stable disease in nine patients and progressive disease (PD) in one patient (3%). The disease control rate (CR+PR+SD) was 97%.

Preservation of the anal sphincter

Prior to therapy, abdominoperineal resection was planned in 11/37 patients who had definitive surgery. Following completion of CRT, sphincter preserving surgery was successfully performed in two of these patients. The SPR was 76% (28/37 patients) and in the subgroup of 17 patients with tumors located within 5 cm of the anal verge, sphincter preservation was possible in nine patients.

Postoperative chemotherapy

Postoperative chemotherapy was administered to 34 patients. Reasons for not administering adjuvant chemotherapy were: death due to sepsis after colonic necrosis and perforation 6 weeks after the operation (one patient); a >8 week interval between the operation and adjuvant therapy (one patient); postoperative complications (one patient).

After a median follow-up of 13.5 months (range; 4.8–25.6 months), three patients had suffered relapse due to systemic progression (one pulmonary spread, one pulmonary and retroperitoneal and one suprarenal). Re-examination of the pretreatment MRI of the pelvis revealed bone metastases in another patient. No local recurrences had occurred.

Discussion

Neoadjuvant cetuximab plus CRT on tumor response in LARC

In this phase II study the addition of cetuximab to capecitabine and radiotherapy in the neoadjuvant treatment of LARC patients led to a pCR rate of 8% and a high rate (73%) of pathological downstaging of tumors. The pCR rate is similar to that reported in a phase I/II study in Belgian LARC patients, (5%), where a lower rate of pathological tumor downstaging (38%) was recorded.²² Similar doses of cetuximab and CRT were used in the two studies, however in the current study capecitabine was administered twice daily at 1250 mg/m² for two weeks, three weeks prior to radiotherapy whereas in the Belgian study a dose escalation of capecitabine was administered twice daily (650 mg/m² or 850 mg/m²) concomitantly with cetuximab and radiotherapy.²² Patient baseline and tumor characteristics were comparable and whether the administration of capecitabine three weeks prior to cetuximab plus CRT leads to higher tumor downstaging in this setting requires further clinical investigation.

More recently a similar pCR (7.7%) was reported in LARC patients receiving neoadjuvant cetuximab given as a single dose and then combined with 5-FU and radiotherapy.²¹ The addition of a second chemotherapeutic agent to neoadjuvant capecitabine-based CRT with cetuximab has not demonstrated a marked improvement to the rates of pCR or tumor downstaging in LARC,²⁴ which remain similar to those reported from studies of neoadjuvant capecitabine-based CRT,^{12,13,25} or capecitabine-based CRT with irinotecan or oxaliplatin.^{26,27}

In the present study an assessment of radiological tumor response according to RECIST criteria was made. An overall response rate of 71% was recorded, which was similar to the that reported for patients with locally advanced SCCHN receiving cetuximab in combination with radiotherapy.¹⁸ The rates of tumor downstaging as determined by MRI and histopathological techniques were similar and reflected the findings from the MERCURY

study where the two techniques were equivalent to 0.5 mm in the assessment of tumor spread in rectal cancer patients.²⁸

Recent studies have focused on the identification of predictive biomarkers for response to treatment with cetuximab. Data from randomized studies in mCRC patients suggest that tumor *KRAS* mutational status is predictive for response to cetuximab in combination with chemotherapy.^{16,17} In rectal cancer patients treated with cetuximab-based therapy, the frequency of TRG3-4 was reported to be higher (58% vs. 7.7%) in patients whose *KRAS* wild-type tumors had a high *EGFR* gene copy number compared with those tumors harboring a low *EGFR* gene copy number.²⁹ Debucquoy and colleagues suggest that decreased tumor proliferation observed in patients receiving an initial dose of cetuximab prior to CRT might affect the subsequent efficacy of capecitabine and RT leading to the low pCR reported.²² Upregulated *EGFR* expression following the initial dose of cetuximab, and the presence of pro-inflammatory changes in tumors sampled at resection was associated with improved patient DFS, suggesting these to be potentially novel predictive markers of cetuximab-based treatment in this setting.³⁰

Neoadjuvant cetuximab plus CRT on sphincter preservation rate

A secondary endpoint of this study was the SPR. All patients received definitive surgery, and 76% underwent sphincter preserving surgery, including 2/11 patients planned to receive abdominoperineal resection prior to neoadjuvant CRT. Within the group of patients receiving sphincter preserving surgery 53% had tumors located within 5 cm of the anal verge. Similar SPR have been reported in patients receiving capecitabine-based neoadjuvant CRT.^{12,13} However an improvement in the SPR in the preoperative CRT arm compared to radiotherapy alone arm has not been conclusively demonstrated in randomized studies.^{5,8}

Toxicity and postoperative complications of cetuximab plus CRT

The combination of cetuximab with capecitabine-based CRT was generally well tolerated with the majority of patients completing the treatment protocol. The most common adverse event was grade 1/2 skin rash, which has also been described in other studies in mCRC investigating cetuximab,^{16,17} and was similar to that previously reported in LARC patients receiving neoadjuvant cetuximab plus CRT as was the frequency of grade 3 diarrhea (11%).²² Radiodermatitis occurred in 16% of patients which was similar to that reported in locally advanced SSCHN where the addition of cetuximab to radiotherapy was found not to significantly increase the incidence of grade 3 radiodermatitis.¹⁸ There were no immediate

postoperative deaths and the majority of the complications were associated with delayed wound healing.

Conclusion

In summary, neoadjuvant cetuximab in combination with capecitabine-based CRT in LARC was well tolerated and whilst pCR rates were not high, a high frequency of tumor downstaging was observed. To date, although preoperative CRT significantly improves local control in LARC, there is no improvement on overall survival compared with adjuvant therapy. To assess the value of EGFR-targeted agents in this setting, future randomized control trials should maybe evaluate the efficacy and safety of these agents with CRT on these endpoints and perhaps in patients assessed for potential predictive biomarkers of efficacy.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgement

The study was sponsored by the Institute of Oncology, Ljubljana and was cosponsored by Merck KGaA (Darmstadt, Germany) who also provided the study drug cetuximab and some editorial assistance.

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Conflicts of interest

There are no conflicts of interest to declare.

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Table 1. Patient and disease characteristics at baseline

Characteristics	Patients (n=37)
Median age, years (range)	55 (33–72)
Gender	
Male	30
Female	7
WHO performance status	
0	26
1	11
TN clinical stage	
T3N0	3
T2N1	1
T3N1	13
T2N2	1
T3N2	15
T4N2	4
Clinical tumor size per MRI, cm	
Median (range)	5 (2.2–9)
Tumor distance from anal verge, cm	
Median (range)	6 (1–11)
Type of surgery ^a	
Anterior resection	3
Low anterior resection	20
Coloanal reconstruction	3
Abdominoperineal resection	11

^aAs planned before the start of preoperative chemoradiotherapy.

MRI, magnetic nuclear imaging; N, node; T, tumor; WHO, World Health Organization.

Table 2. Acute toxicity of preoperative chemoradiotherapy in the safety population (n=37)

	Toxicity ^a , n		
	Grade 1	Grade 2	Grade 3
Hematological			
Leukocytopenia	2	3	-
Anemia	-	1	-
Gastrointestinal			
Diarrhea	4	4	4
Anorexia	-	3	1
Fatigue	-	3	-
Nausea	1	1	-
Metabolic/laboratory			
Hepatotoxicity	4	3	1
Hypoalbuminemia	-	2	-
Hypokalemia	1	-	-
Other			
Acneiform rash	20	12	-
Radiodermatitis	7	8	6
Hand and foot syndrome	8	6	-
Dry skin	9	1	-
Infection	1	3	1
Allergic/hypersensitivity	1	2	2
Cystitis	1	-	-

According to National Cancer Institute Common Toxicity Criteria (version 3)

Table 3. Surgery and perioperative complications (n=37)

Parameter	Number of patients
Surgery	
Low anterior resection	25
Abdominoperineal resection	9
Coloanal anastomosis	3
Perioperative complication	
Delayed healing of postoperative wound	6
Cystitis	2
Incarcerated transversostoma	1
Sepsis	1
Anastomic leakage/ abdominal abscess	1
Bronchopneumonia	1
Febrile episode	1

Table 4. Distribution of postoperative pathological TMN stages compared with pretreatment clinical stages (n=37)

Preoperative TMN stage	Postoperative TMN stage									
	T0N0	T1N0	T2N0	T3N0	T4N0	T0N1	T2N1	T2N2	T3N1	T3N2
T3N0	1	1	1	-	-	-	-	-	-	-
T2N1	-	-	1	-	-	-	-	-	-	-
T3N1	1	1	6	3	-	1	-	-	1	-
T2N2	-	-	-	-	-	-	1	-	-	-
T3N2	1	1	3	4	-	-	-	1	4	1
T4N2	-	-	1	1	1	-	-	-	1	-
Total	3	3	12	8	1	1	1	1	6	1

Shading denotes where tumors demonstrate overall stage downstaging.
M, metastases; N, node; T, tumor

Figure legend**Figure 1. A summary of the study treatment**

CT, computed tomography; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; US, ultrasonography

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Figure 1 Study protocol

