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Neo-adjuvant treatment of rectal cancer with capecitabine and oxaliplatin in combination with radiotherapy: a phase II study

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Background: Preoperative chemoradiation is now standard treatment for stages II–III rectal cancer. Capecitabine (CAP) and oxaliplatin (OX) are synergistic with radiotherapy (RT) and active in colorectal neoplasms.

Patients and methods: Two cycles of CAP 825 mg/m^2 b.i.d. (days 1–14) and OX 50 mg/m^2 (days 1 and 8) every 3 weeks were given concomitantly with pelvic conformal RT (45 Gy). Patients with a ≥T3 and/or node-positive rectal tumour were eligible. The pathologic tumour response was defined according to the tumour regression grade (TRG) scale.

Results: Forty-six patients were enrolled. Gastrointestinal adverse events were mostly G1–G2; only two patients experienced G3 vomiting and diarrhoea and six patients had G1 peripheral neuropathy. Haematological toxicity was rare. G2 proctitis and anal pain occurred in two patients. Pathological complete response (TRG1) was observed in nine patients (20.9%; 95% CI 8.7%–33.1%); TRG2 in 19 patients (44.2%); TRG3 in 12 patients (27.9%); and TRG4 in three patients (7%). Overall, nine patients recurred: five with distant metastases, one with local recurrence, and three with both local recurrence and distant metastases.

Conclusions: CAP–OX–RT as preoperative treatment for rectal cancer induces a remarkable rate of complete or near-complete pathologically documented response and is well tolerated.

Key words: chemoradiotherapy, neo-adjuvant, rectal cancer

introduction

Colorectal cancer is the fourth most frequent neoplasia worldwide, representing the third cause of death among men and women [1]. About one-third of large bowel tumours are represented by rectal cancers.

Although surgery (total mesorectal excision—TME) still plays a fundamental role in the treatment of rectal cancer, a multidisciplinary strategy, consisting in radiotherapy (RT) and chemotherapy, results in significantly improved local control and overall survival (OS) [2–4]. Several studies and two meta-analyses demonstrated that, compared with surgery alone, preoperative RT significantly reduces the risk of local recurrence and cancer-specific mortality [5, 6]. The benefit on local control derived from the addition of RT to surgery alone is maintained even when the best surgical technique (i.e. TME) is carried out [7]. Two recent phase III trials demonstrated that the addition of chemotherapy [5-fluorouracil (5-FU) modulated by leucovorin] to preoperative conventionally fractionated RT alone significantly improves local control, but neither study showed an advantage in terms of survival [8, 9], suggesting that more intense chemotherapy is needed to prevent distant metastases and, therefore, to reduce mortality.

The issue of the best timing for chemoradiotherapy (before or after surgery) was addressed in a large phase III trial conducted by the German Rectal Cancer Study Group, which demonstrated that preoperative treatment halves local recurrence (6% versus 13%) and significantly reduces G3–G4 acute toxicity (27% versus 40%) versus postoperative treatment [10].

Several retrospective analyses suggest that the pathological stage of disease after neo-adjuvant treatment and/or the tumour regression rate have a significant prognostic impact on disease-free survival (DFS) and OS [11–13], thereby stimulating the evaluation of chemoradiotherapy regimens that produce high response rates with limited toxicity. In this context, a meta-analysis investigated the predictive role of different

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chemoradiotherapy regimens on the occurrence of a pathological complete response (pCR) and showed that a chemotherapy regimen consisting in continuous infusion of 5-FU or capecitabine (CAP), two antineoplastic drugs, and a dose of RT ≥45 Gy are significantly associated with a higher rate of pCR [14].

CAP is a an oral fluoropyrimidine that is converted in 5-FU mostly in neoplastic tissues exploiting the higher activity of the enzyme thymidine phosphorylase in tumour cells, and it mirrors the pharmacokinetic effects of 5-FU by continuous infusion. CAP showed a similar efficacy and a better tolerability compared with the combination of 5-FU + folinic acid (FA) both in metastatic and in adjuvant treatment of colorectal cancer. In patients with locally advanced rectal cancer, preoperative CAP with concomitant RT is effective; in fact, it resulted in downstaging of the primary tumour and/or regional lymph nodes in about 35%–75% of patients and in a pCR in about 10%–20% of cases [15].

The addition of oxaliplatin (OX) to 5-FU–FA resulted in a significant improvement in outcome in patients with metastatic colorectal cancer [16]. Also in the adjuvant setting, it significantly prolonged DFS [17] and OS [18] of stage III colon cancer patients, with a manageable overload in toxicity. Moreover, the results of five recent trials indicate that, at least in metastatic disease, the combination of CAP plus OX is equivalent to 5-FU–FA plus OX [19–23].

Since both CAP and OX have radiosensitising effects [24, 25] and are synergistic in colorectal cancer, research efforts focused on treatment schedules that included both drugs and RT as neo-adjuvant treatment of rectal cancer patients. In 2003, a German phase I/II trial demonstrated the feasibility and the activity of preoperative RT with concurrent CAP and OX in patients with T3–T4 rectal cancer [26]. In the phase I part of the study, dose-limiting toxicity was diarrhoea and the recommended dose of OX was 50 mg/mq in combination with CAP, 825 mg/m^2 b.i.d. on days 1–14 and 22–35, and 50.4 Gy of RT. All the 32 patients enrolled in the phase II part of the trial achieved downstaging of the primary tumour and 19% obtained a pCR.

Based on these considerations, in 2004, we designed a phase II trial aimed to verify the activity in terms of pCR of the combination of CAP + OX + RT in the preoperative treatment of stages II–III rectal cancer patients. Secondary end points were the evaluation of tolerability, recurrence-free survival and OS.

patients and methods

patients selection

Patients were eligible if they met the following criteria: histological diagnosis of rectal adenocarcinoma invading through the intestinal wall or with pelvic lymph node involvement as measured by endorectal ultrasonography (uT3/uT4 or any uT/N+); no distant metastases; age >18 years; Eastern Cooperative Oncology Group performance status zero to one; blood cell count within normal values; normal liver and renal functioning (if creatinine was at upper normal values, creatinine clearance should be ≥60 ml/min). Informed consent was obtained by all patients before trial enrolment. Rectal tumour was defined as a lesion with the distal border ≤12 cm from the external anal verge as measured by a rigid rectal probe. Perirectal lymph nodes were considered metastatic when hypoechoic and ≥5 mm in diameter at endorectal ultrasonography.

The main exclusion criteria were as follows: pregnancy or breast-feeding; no effective contraception; comorbidities (angina, acute myocardial infarction within the previous 5 years, arrhythmia, history of neurological or psychiatric disorders, bowel inflammatory chronic disease); and previous RT.

treatment

CAP was given orally at 825 mg/m^2 b.i.d. (two administrations each 12 h apart), from day 1 to 14 every 21 days. OX was administered i.v. at 50 mg/m^2, diluted in 500 ml of glucose solution as a 120-min infusion, at days 1 and 8 of each 21-day cycle. CAP was withheld in case of ≥G2 vomiting, not responsive to 5HT3 antagonists; ≥G2 diarrhoea, not responsive to loperamide; absolute neutrophil count (ANC) <1000/mmc; and platelets count <100 000/mmc. In case of toxicity present the programmed day of OX infusion, the following rules were applied: ANC <1500/mmc wait until ANC ≥1500/mmc; platelets count <100 000/mmc wait until platelets count >100 000/mmc; and diarrhoea >G1 wait until diarrhoea ≤G1. RT was delayed in case of grade ≥3 toxicity. Treatment must be stopped in case of G4 toxicity.

Pelvic conformal RT was delivered at the daily dose of 1.8 Gy, 5 days a week, up to 45 Gy in 5 weeks. Briefly, CT (computed tomography) simulation was carried by a continuous CT scan (Lybra Esaote, Italy) with patients in prone position using a vacuum locked mattress. CT images were electronically transferred to the Focal Ease 4.2 CT Simulation software (Computerized Medical System, Inc., St Louis, MO) for target and critical organs (small bowel, bladder, and anal sphincter) contouring. Treatment planning was done by a three-dimensional planning system (XiO 4.2, Computerized Medical System, Inc., St Louis, MO). A three-shaped field technique was designed using a 10/20 MV photon posterior–anterior field and 20 MV photon opposed wedged lateral fields.

After surgery, further 4 months of adjuvant chemotherapy with CAP or weekly 5-FU–leucovorin were proposed to all the patients. The oral (CAP) or the i.v. (5-FU–leucovorin) regimen was a patient choice.

evaluation criteria

Staging procedures had to be carried out within the 2 weeks preceding the treatment start and included blood cell count, biochemistry, blood carcinoembryonic antigen level, thorax–abdomen–pelvis CT scan, total body positron emission tomography (PET), colonoscopy, and endorectal ultrasonography.

At 4–6 weeks after chemoradiotherapy completion, the stage of the disease was re-evaluated by repeating thorax–abdomen–pelvis CT scan, total body PET, and endorectal ultrasonography, in order to assess primary tumour response and to exclude the presence of distant metastases.

Patients were monitored weekly by history, physical examination, and blood count; complete biochemistry was carried out at each cycle. Toxicity was graduated according to National Cancer Institute Common Toxicity Criteria, version 3.0.

surgery and pathology

The protocol suggested surgery be carried out 6–8 weeks after completion of RT, using the total mesorectal excision technique. However, the choice of the surgical procedure (i.e. abdominoperineal resection or low anterior resection) was at the surgeon's discretion as it was the bridge ileostomy after low anterior resection.

Specimen dissection and mesorectum evaluation were carried out according to the College of American Pathologists protocol for all invasive carcinomas of the colon and rectum (revised version of January 2005; based on AJCC/UICC TNM, 6th edition). Tumour sampling was carried out along the neoplasm major axis; mesorectum was always inked and sampling was carried out in the points of maximum neoplastic infiltration.

Pathologic response was independently scored by two pathologists (FPDA and MRDA) who did not participate in the clinical data gathering, following tumour regression grade (TRG) as described by Mandard [27] (see Table 1).

study design

This was a two-step phase II study, according to the Simon design [28], whose primary end point was the pCR rate. Based on previous results, 10% pCR was defined as null hypothesis (H0) and a pCR rate ≥25% as alternative hypothesis (H1). With an alpha error = 0.05 and a study power of 80%, at least three pCRs were required among the first 18 patients (first step), and at least eight pCRs in a total of 43 patients (second step) should be observed to reject H0 and accept H1.

The protocol was approved by the Ethics Committee of the School of Medicine of the University of Naples 'Federico II'.

results

From August 2004 to December 2007, 46 patients were enrolled, with a median age of 64 years (range 42–79). Patients and baseline tumour characteristics are listed in Table 2. Twenty-seven cases (58.7%) were classified as node positive by endorectal ultrasonography; in two cases, due to stenotic rectal tumour, perirectal fat could not be fully explored with ultrasonography, but a pelvis nuclear magnetic resonance confirmed the presence of enlarged perivisceral lymph nodes. In half the patients, the primary tumour was located in the lower portion of the rectum (≤6 cm from the external anal verge).

activity

Thirty-six of the 46 treated patients (78.3%) underwent both pre- and posttreatment endorectal ultrasonography and were accessable for radiological downstaging assessment. After chemoradiotherapy, there was a remarkable increase of node-negative [27 of 36 patients (75%) versus 13 of 36 (36.1%)] and of uT1–T2 tumours [10 of 36 (27.8%) versus 5 of 36 (13.9%)].

Forty-three patients underwent surgery (one refused surgery, one developed lung metastases when restaged after chemoradiotherapy, and one died from causes unrelated to toxicity or tumour progression). Median time from the last administration of RT to surgery was 8.4 weeks (range 5–11.4 weeks). Twenty-eight (65.1%) underwent low anterior resection (21 with bridge ileostomy), 11 patients (25.6%) abdominoperineal resection with permanent colostomy, two (4.6%) patients Hartmann resection, and one patient received a trans-sphincteral resection; in a 76-year-old patient, with a tumour located immediately above the external anal verge, the surgeon opted for a trans-anal removal of the residual disease. All 43 operations were defined as R0 by the surgeon.

Pathological findings of the surgical specimens are illustrated in Table 3: in all 43 operated patients, the circumferential resection margin was free from tumour cells; the median number of examined lymph nodes was 7.5 (range 0–20) and

Table 1. Tumour regression grade scoring system

TRG 1	Complete response with absence of residual cancer and fibrosis extending through the wall
TRG 2	Presence of residual cancer cells scattered through the fibrosis
TRG 3	Increase in the number of residual cancer cells, with fibrosis predominant
TRG 4	Residual cancer outgrowing fibrosis
TRG 5	Absence of regressive changes

Table 2. Patients and tumour characteristics

	n	%
Gender		
Males	30	65.2
Females	16	34.8
ECOG performance status		
0	44	95.7
1	2	4.3
Primary tumour stage		
uT4/N−	2	4.3
uT4/N+	4	8.7
uT3/N−	15	32.6
uT3/N+	19	41.3
uT3/Nx	1	2.2
uT2/N+	4	8.7
uT2/Nx	1	2.2
Distance from external anal verge		
<3 cm	4	8.7
3–6 cm	19	41.3
6.1–9 cm	17	36.9
9.1–12 cm	6	13.1

ECOG, Eastern Cooperative Oncology Group.

Table 3. Postsurgical pathological results

	n	%
Tumour regression grade ($n = 43$)		
1	9	20.9
2	19	44.2
3	12	27.9
4	3	7.0
Histotype ($n = 34$)		
Adenocarcinoma	29	95.7
Mucinous	5	4.3
Pathological stage ($n = 43$)		
ypT0, N0	9	20.9
ypT1, N0	2	4.6
ypT1, N1	1	2.3
ypT2, N0	16	37.2
ypT3, N0	6	13.9
ypT3, N1	6	13.9
ypT1, Nx[a]	1	2.3
ypT2, Nx[b]	1	2.3
ypT3, Nx[b]	1	2.3

[a]One patient received trans-anal resection without lymph node dissection.
[b]In 2 cases, no lymph nodes were isolated from the perirectal fat.

about two-thirds of patients were node negative; in nine cases (20.9%; 95% CI 8.7%–33.1%), no viable tumour cells were found in the bowel wall; and in 19 other patients (44.2%), only scattered tumour cells were identified in the bowel wall where strata were replaced by fibrosis and inflammatory infiltrate. Thus, a total of 28 patients (65.1%) achieved a pathological complete (TRG1) or near-complete response (TRG2). Regressive changes (such as fibrosis or inflammatory infiltration) were noted in all examined surgical specimens; in fact, no TRG5 was recorded.

A comparison of the pretreatment ultrasonographic stage with the postsurgical pathological stage showed a final downstaging rate of 76.3% for the uT3–T4 primary tumours, and 77.8% of uN+ patients were pN− (Table 4).

toxicity

All 46 patients completed the planned programme of RT; median duration was 5 weeks (range 4.6–7.1 weeks). To complete the 25 administrations of RT, 2 of 46 patients took 7 and 6 weeks, respectively: one due to linear accelerator failure and one due to toxicity (vomiting and diarrhoea) that occurred during the first cycle of treatment.

Forty-five patients received the two planned cycles of chemotherapy without any dose reduction; one patient, who experienced G2 diarrhoea and G1 vomiting during the first cycle, refused further chemotherapy and, after toxicity recovery, continued with RT alone; only one patient delayed day 1 of the second cycle due to neutropenia. Overall, the combined treatment was well tolerated, no grade 4 toxicity was recorded and the incidence of diarrhoea was limited. The profile of the adverse events occurred to the 46 patients along the combined chemoradiotherapy treatment is depicted in Table 5. As expected, toxicity was slightly more frequent at the second cycle: 60% of the total number of adverse events refers to cycle 2.

Six patients experienced major postoperative complications: ureteral stenosis requiring the placement of ureteral stent (one patient); fistula with vagina, which soon regressed without surgical re-intervention (one patient); ureteral stenosis with hydronephrosis treated with pyelostomy (one patient); fistula with bladder (two patients) fistula with bladder plus ureteral stenosis requiring re-operation (one patient).

outcome

After radical surgery, 39 patients received adjuvant chemotherapy (35 CAP and four 5-FU plus leucovorin); four patients never started adjuvant chemotherapy, due to patient refusal (1), toxicity experienced during neo-adjuvant treatment (1); two patients, without postsurgical complications, referred again to the medical oncology department >4 months after surgery.

On 30 June 2008, at a median follow-up of 28 months, 9 of the 46 patients (19.5%) relapsed and four died (one for reasons not related to toxicity or tumour progression and three due to metastatic disease). One patient had local recurrence; five patients distant metastases (two lung, two liver, one abdominal); and three patients experienced both local recurrence and distant metastases (liver, lung, and central nervous system plus bone, respectively).

The ypTN stage of the nine relapsed patients was as follows: ypT3N0 (two cases: distant metastases); ypT3N1 (two cases: both local recurrence and distant metastases); ypT2N0 (one local recurrence and one distant metastases); ypT3Nx (one case: both local recurrence and distant metastases); ypT1N0 (one case: distant metastases); and one patient had disease progression when restaged after chemoradiotherapy, and thus did not undergo surgery (the pretreatment stage was uT3N−).

discussion

Stages II and III rectal cancer requires a multidisciplinary treatment approach, namely surgery, RT, and chemotherapy, in order to achieve optimal local control and prolonged DFS and OS.

Several studies have correlated long-term prognosis with TRG [11, 12, 29] and with a pCR after preoperative chemoradiotherapy [30–32] that remains the most objective factor with which to evaluate the activity of neo-adjuvant treatment because imaging techniques have limited specificity in distinguishing between fibrosis and inflammatory changes of the bowel wall and tumour invasion. However, it must be noted that the pathologist who carries out the regression grade scoring should be expert and motivated to find residual tumour cells in the bowel wall and to single out viable from nonviable cells.

The present study confirms that chemoradiotherapy with CAP and OX is very active as preoperative treatment for rectal cancer patients. Indeed, it induced a complete pathologically documented response (pathological response) in 20.9% of patients and a near-complete pathological response in a further 44.2% of cases. An additional remarkable finding is the high tolerability of the regimen and the very low incidence of moderate or severe acute gastrointestinal toxicity. Table 6 summarized the main results of our study in comparison with previous phase II trials investigating the activity and the tolerability of neo-adjuvant chemoradiotherapy with CAP and

Table 4. Tumour and lymph nodes downstaging (no. of patients)

	pT0	pT1	pT2	pT3	pT4	Total		pN0	pN1	pNx	Total
uT4	1	0	3	2	0	6	uN+	21	5	1	27
uT3	6	4	13	9	0	32	uN−	11	2	2	15
uT2	2	0	1	2	0	5	uNx	1	0	0	1
Total	9	4	17	13	0	43	Total	33	7	3	43

OX in rectal cancer patients. The pCR rate is similar in all studies, but the incidence of G3–G4 diarrhoea ranges from 30% to 2.2%. In most studies [33, 36–39], CAP was administered continuously for 5 days/week, at a dose of 725–825 mg/m^2 b.i.d. in combination with weekly OX. This regimen, at least in theory, is the best schedule to exploit the synergistic effect with RT. However, the pCR rate was poor (12%–14%) when combined with 45 Gy of radiation [33, 37, 39] and reached 20%–25% [36, 38] when RT dosage was 50.4 Gy. On the other hand, the incidence of G3–G4 diarrhoea was relevant (9%–30%), irrespective of radiation dosage. In the remaining two studies, CAP was scheduled for 2 weeks 'on' followed by 1 week 'off'. Patients enrolled in the Dutch trial [35] received a higher dose of CAP (1000 mg/m^2 b.i.d.) and a very low dose of OX (85 mg/m^2 days 1 and 29). In that trial, pCR was poor (only 9.5%) and 18.2% of patients experienced G3 diarrhoea. The trial conducted by the German group [34] used a lower dose of CAP (825 mg/m^2 b.i.d.) and a higher dose of OX (50 mg/m^2 days 1, 8, 22, 29) and reported a pCR in 16% of cases and G3–G4 diarrhoea in ~12% of patients. The treatment schedule we used was very similar to that used in the German trial, except for the dose of RT (45 Gy instead of 50.4 Gy), and we obtained a very high rate of pCR (20.9%) whereas only one patient experienced grade 3 diarrhoea. In summary, although we cannot rule out that the results in terms of activity and toxicity of these phase II trials are due to chance, due to the limited sample size, we can also argue that they are (at least in part) due to the used schedule.

Table 5. Worse experienced toxicity among 46 treated patients

Adverse event	G0 (*n*)	G1 (*n*)	G2 (*n*)	G3 (*n*)
Nausea	35	10	1	–
Vomiting	39	5	1	1
Diarrhoea	31	8	6	1
Stomatitis	45	1	–	–
Leukopenia	43	2	1	–
Anemia	45	1	–	–
Thrombocytopenia	43	3	–	–
Peripheral neuropathy	40	6	–	–
Asthenia	38	8	–	–
Rectal tenesmus	34	12	–	–
Anal pain	37	8	1	–
Proctitis	38	7	1	–

The acute and late postsurgical side-effects of short-term RT were exhaustively studied in patients enrolled in the Dutch trial [40]; in that trial, morbidity and complications were slightly more frequent in the RT arm (mostly due to perineal wound healing) compared with surgery alone. In our trial, the major postoperative complications were fistulas and ureteral stenosis, and their incidence coincides with that reported by others [33, 34, 36]. Notably, there were no infective complications, such as pelvis abscesses or wound dehiscences. Interestingly, our patients were treated by the same medical oncologist team and the same team of radiotherapists, but, after neo-adjuvant treatment, they were operated on by seven different surgeons, most of whom were specialists in colorectal surgery and the others were specialist in abdominal surgery. This is a very positive aspect because it is a scenario that, within a clinical trial, is similar to clinical practice.

In conclusion—although the definite advantage for DFS and OS of the addition of OX to fluoropyrimidine alone in the treatment of rectal cancer and the definition of the most

Table 6. Comparison of the published phase II study using capecitabine–oxaliplatin in combination with preoperative radiotherapy

Author	Treatment schedule	Eligible patients	pCR (%)	G3 diarrhoea (%)	G4 diarrhoea (%)
Machiels et al. [33]	RT 45 Gy; CAP 825 mg/m^2 b.i.d. × 5 days/week; OX 50 mg/m^2 weekly × 5 weeks	T3–T4 and/or N+ (*n* = 40)	14	30	
Rödel et al. [34]	RT 50.4 Gy; CAP 825 mg/m^2 b.i.d. days 1–14 and 22–35; OX 50 mg/m^2 days 1, 8, 22, and 29	T3–T4 and/or N+ (*n* = 103)	16	10.6	1
Hospers et al. [35]	RT 50.4 Gy; CAP 1000 mg/m^2 b.i.d. days 1–14 and 25–38; OX 85 mg/m^2 days 1 and 29	T3–T4 (*n* = 22)	9.5	18.2	–
Fakih et al. [36]	RT 50.4 Gy; CAP 725 mg/m^2 b.i.d. × 5 days/week; OX 50 mg/m^2/weekly × 5 weeks	Stages II–III (*n* = 25)	24	20	–
Rutten et al [37]	RT 45 Gy; CAP 825 mg/m^2 b.i.d. × 5 days/week; OX 50 mg/m^2 weekly × 5 weeks	T3–T4 (MNR) (*n* = 85)	13	12	4
Alonso et al. [38]	RT 50.4 Gy; CAP 825 mg/m^2 b.i.d. × 5 days/week; OX 50 mg/m^2/week × 6 weeks	T3–T4 or N+ (*n* = 67)	19.4	25	
Majem et al. [39]	RT 45 Gy; CAP 825 mg/m^2 b.i.d. × 5 days/week; OX 50 mg/m^2/weekly × 5 weeks	T3–T4, N−/N+ (*n* = 45)	12	9	–
Present study	RT 45 Gy; CAP 825 mg/m^2 b.i.d. days 1–14 and 22–35; OX 50 mg/m^2 days 1, 8, 22, and 29	uT3–T4 or uN+ (*n* = 46)	20.9	2.2	–

pCR, pathological complete response; RT, radiotherapy; CAP, capecitabine; OX, oxaliplatin; MNR, magnetic nuclear resonance.

effective adjuvant chemotherapy remains to be established and is pending the results of ongoing phase III trials (NSABP-R04, FNCLCC-ACCORD-12/0405, PETACC-6, and CAO/ARO/AIO-04)—overall, phase II studies agree that the CAP–OX combination is very active; it allows R0 resection in most patients and induces a pCR in ~20% of patients. However, acute toxicity seems to depend on treatment schedule, thus drug dosage and scheduling should be carefully selected. The regimen we used, which was first set up by Rödel (i.e. CAP for 2 weeks followed by 1 week off and OX at days 1 and 8), combined with 45 Gy of conformal RT, is very active and has excellent tolerability.

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