Capecitabine chemoradiation in the preoperative treatment of patients with rectal adenocarcinomas: a phase II GERCOR trial

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Abstract

Background: X CRT is attractive since the active metabolite, 5-FU, is a potent radiosensitizer. There is a strong preclinical rationale based on higher TP levels in tumor, which are further upregulated with radiation, TP being the final metabolising enzyme of X to 5-FU. X has potential to enhance the results of rectal cancer CRT. A phase I study recommended X 825 mg/m² twice daily with pelvic RT. **Methods:** We conducted a multicenter, phase II trial to evaluate the efficacy of pre-operative X CRT in pts with adenocarcinoma of the lower or middle third of the rectum, suitable for curative surgery, T3-T4 or N+. Pts had no inflammatory bowel disease, adequate biological parameters, written informed consent. RT delivered 45 Gy in 25 fractions over 5 weeks. X was taken 7 days/week, 825 mg/m² morning and evening, throughout RT. Surgery was 5 to 7 weeks after the end of RT. The primary endpoint was complete histological response rate; secondary endpoints were downstaging and tolerability. **Results:** From July 2002 to June 2003, 51 pts were included, 17 women and 34 men, median age 62 years [35-78], with median KPS (Karnofsky) 90% [80-100]. Sixty three percent of tumors involved the lower third of the rectum, 45% were fixed.. Initial endoscopic US/MRI classification was T2, T3, T4 in 4, 45 and 1 cases respectively, 1 pt was T3 on CT evaluation. Median delivered dose was 45 Gy [39,6-45 Gy] in 32 to 44 days. RT was temporarily interrupted in 3 pts (2 G3, 1 G2 skin reaction + G2 diarrhoea in 1) and X stopped before the end of RT in 2 pts (2 G2 hand-foot syndrome + G3 diarrhoea in 1). Adverse events were mostly gastrointestinal (10 pts G2, 3 pts G3 diarrhoea) and cutaneous (8 pts G2 and 2 pts G3 local skin reaction); 3 pts experienced G2 hand-foot syndrome. Fifty pts had surgery (29 conservative), 1 refused. Histopathology revealed 24% complete responses (95% CI 12-36%), 12% persistence of only minimal tumor cell foci and 23% additional T downstaging. Resection margins were tumor free in 100%. **Conclusions:** X CRT is well tolerated and efficacy supports further exploration, as a single agent and as part of new therapeutic strategies with chemo- and biological therapies.

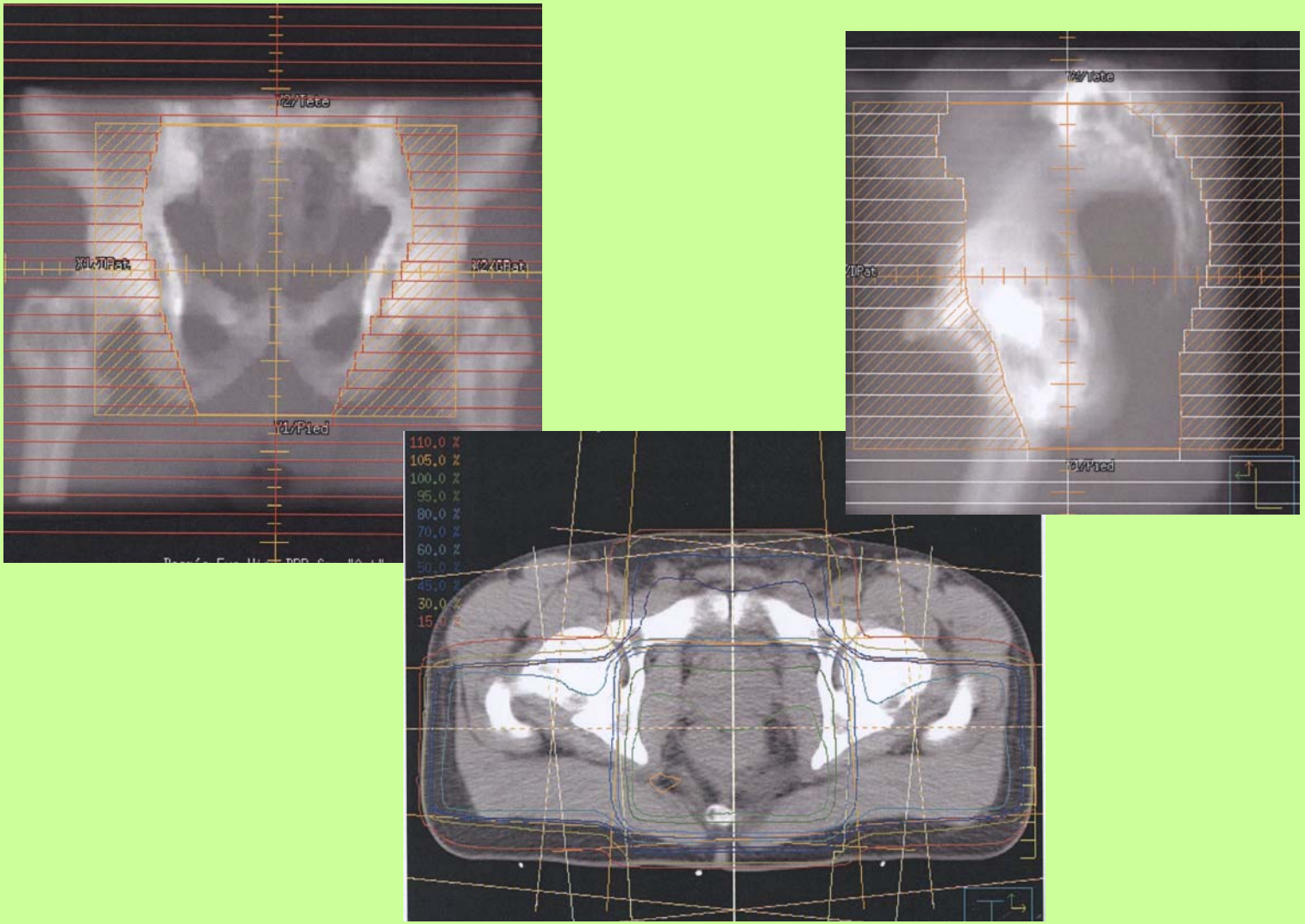
Pré-operative capecitabine and radiotherapy in rectal cancer: rationale

- Pre-operative radiotherapy (RT) improves both local control and survival in rectal cancer [1]
- Addition of 5-FU chemotherapy may inhance these results and increase the possibility of conservative surgery [2]
- Capecitabine (X) is an oral fluoropyrimidine carbamate which is metabolised in 5-FU, the final enzyme being thymidine phosphorylase [3]
- Thymidine phosphorylase is overexpressed in tumor and is upregulated with radiation
- Twice daily oral administration of capecitabine mimics continuous infusion 5-FU
- Phase I study demonstrated that chemoradiation (CRT) with capecitabine and pelvic radiotherapy was feasible and recommended the dose of 825 mg/m² twice daily [4]

X CRT in rectal cancer: study design

- **Multicentric, non randomised Phase II trial**
- **Eligibility**
  - Adenocarcinoma of the lower of middle third of the rectum
  - US/MRI classification T3/T4 or N+, suitable for curative surgery
  - KPS ≥ 60%, no bowel inflammatory disease, no coronaropathy, adequate biological parameters
- **Treatment:**
  - Radiotherapy delivered 45 Gy in 25 fractions over 5 weeks, using 3 or 4 beams from high energy linear accelerator
  - Capecitabine was started the first day of RT at a dose of 825 mg/m² twice daily and continued through the end of RT
  - Surgery was performed 5 to 7 weeks after the end of RT
- **Endpoints:**
  - Primary: complete histologic response rate
  - Secondary: tolerance (NCI CTC), tumor downstaging, sphincter preservation rate

Typical fields arrangement for lower rectal cancer



Tumors were mainly advanced

Table 1: Characteristics of patients and disease at baseline (N=51)

Median age, years (range)	62 (35-78)
Male/female	34/17
Median KPS (range)	90 (80-100)
US/MRI* T stage	T2: 4/ T3: 45/ T4: 1
US/MRI* Nodal involvement (%)	57
Clinical fixation of tumor (%)	45
Tumor extension to the lower third of the rectum	32
Not suitable for sphincter preservation at initial evaluation	21

* 1 pt was staged T3N0 with TDM

Protocol deviation were rare

Table 2: Treatment received

Median radiation dose, Gy (range)	45 (39,6, 45)
Median duration of RT, days (range)	36 (33, 49)
X prematurely interrupted, nb. patients	2

X CRT was a well tolerated regimen

Table 3 : toxicity

N = 51	Grade 1	Grade 2	Grade 3
Nausea/vomitting	12	2	-
Diarrhoea	17	10	3
Asthenia	13	8	1
Skin reactions (pelvis)	15	8	2
Mucositis (pelvis)	7	6	-
Hand-foot syndrome	3	3	-
Anemia	20	4	-
Neutropenia	10	2	-

Surgery

- **50 patients** underwent surgery, 1 patient refused
- **Conservative surgery** was possible in 29 patients

- **Postoperative complications were infrequent:** 1 peritonitis, 1 septicemia, 1 bowel obstruction, 1 perineal abscess, 2 urinary infections, 1 abdominal hernia, 1 colostomia stenosis
- **Reintervention** was necessary in 2 patients

Efficacy judged from pathological response was high

- **Complete pathological response :** 12 (24%) ; (95% CI 12-36%)
- **Persistence of only minimal tumor foci :** 6 (12%)

- **Persistence of tumor :**
  - With downstaging: 12 : 1 pT1, 10 pT2, 1 pT3
  - Stable: 17
  - Progression: 3

- **Number of nodes resected**, median (range): 8 (0-23)
- **Pathologic specimen with involved nodes :** 7 pN1, 4 pN2

- 5 patients which initial surgical indication was amputation (3) or was indeterminate (2) underwent a sphincter preservation procedure

Conclusion

- CRT with continuous twice daily capecitabine (825 mg/m²) is a well tolerated and convenient regimen
- The complete pathologic rate compares favorably with other experiences of 5-FU CRT [5-10] and seems superior than with radiotherapy alone [11, 12]
- This efficacy supports further evaluation, as a single agent and as part of new therapeutic strategies with chemo- and biological therapies

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