

# Evaluation of DOWNSTAGING as leading concept in sphincter-saving surgery for rectal cancer after Preoperative Radio-Chemotherapy (Preop RCT)



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## Introduction

Surgery is still considered the first choice in rectal cancer management (1). Multiple options allow at present to perform a sphincter saving surgery, but this goal must always be joined with a correct oncological treatment. A wide excision of the tumor including in many cases hypogastric and pelvic nerves damage could be effective in order to get this purpose. In the most of cases, however, surgical treatment alone is not enough effective, and a Radiotherapy (RT) with or without Chemio-Therapy (RCT) must be associated. Major results of neoadjuvant RT, compared to postoperative RCT, can be found out especially in high dose protocols (2) and in association with 5-FU administration as radiation enhancing drug. An accurate prestaging, including the DRE and imaging techniques such as ERUS, CT and ER-MRI, allows to schedule patients for a preoperative RT, with a decreasing overtreatment risk, but at present doesn't exist any technique which can detect a pT0N0 tumor.

We have focused the attention on the "downstaging", a new concept in rectal tumor definition, which leads to a complete disappearance of the tumor in 8-26% of surgical specimens. This allows to perform a sphincter saving operation in selected cases, without postoperative morbidity. This evaluation appears to be difficult since

## Abstract

**Aim:** To evaluate the downstaging of rectal cancer after preop R±CT.

**Methods:** 392 patients (pts) with rectal cancer were observed. Only 172 pts (58%) with II and III stage cancer of middle and lower third were examined. Enrol-led pts were 168: 52 of them received preop R±CT (32 RT, 20 R+CT). Preop R±CT group included 14 middle third cancers (73%), 38 lower third (17%). In this group, tumor stage was as follows: 44 T3 stage tumors (86.4%), 8 (15.4%) T4. Mean age of this group was 57 years (range 42-67). Patients received 45 Gy for 5 weeks in 25 fractions and continuous administration of 5-FU (300-500 mg/m<sup>2</sup>/die). Surgery was performed 6 weeks ± 7 days after the therapy.

**Results:** Downstaging, at least of 1 T-stage level, was detected in 45 patients (86%) (8 middle third; 32 lower third); in 5 (9.6%) (4 middle third, 1 lower third), tumor decreased to pT0N0, while in 7 (13.5%) (2 middle third, 5 lower third), there was no response. An Anterior Resection (AR) was performed in 40 patients (77%) [4 Downstaged to pT0N0 middle third cancers; 36 downstaged but with residual disease (8 middle third, 28 lower third)]; APR was performed in 12 (23%) (7 No responders patients, 1 Downstaged to pT0N0 lower third cancer, 4 downstaged but with residual disease of lower third).

**Conclusions:** Preop R±CT is effective in obtaining a significant downstaging to allow sphincter saving surgery, without compromising oncological results.

**Key words:** Rectal cancer, preoperative radiochemotherapy, sphincter saving surgery.

## Riassunto

VALUTAZIONE DELL'EFFICACIA DELLA RADIO-CHEMIOTERAPIA PREOPERATORIA NEL CA DEL RETTO MEDIO BASSO

**Scopi:** Valutare il downstaging dopo R±CT neoadjuvante (preop R±CT) per carcinoma del retto medio-basso.

**Materiali e metodi:** Nel periodo 1994-2000, sono stati osservati 392 pazienti (pts), di cui 52 hanno ricevuto preop R±CT (32 RT, 20 R+CT). Dei 52 pts, 14 erano cancri

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del terzo medio (73%), 38 del retto basso (17%). La divisione per stage è di seguito riportata: 44 tumori T3 (86.4%), 8 (15.4%) T4. L'età media è di 57 anni (range 42-67). 1 paziente hanno ricevuto 45 Gy per 5 settimane in 25 frazioni ± infusione continua di 5-FU (300-500 mg/m<sup>2</sup>/die). L'intervento chirurgico è stato eseguito 6 settimane ± 7 giorni dopo la terapia.

Risultati: Il Downstaging, di almeno uno stadio del T, è stato riscontrato in 45 pts (86%) (12 terzo medio; 33 terzo inferiore); in 5 (9.6%) (4 terzo medio, 1 terzo inferiore) la regressione del tumore è stata totale (pT0N0). In 7 casi (13.5%) (2 terzo medio; 5 terzo inferiore) non è stata riscontrata alcuna risposta. L'intervento di resezione anteriore (RA) e, quindi, la preservazione degli sfinteri, è avvenuta in 40 pts (77%) [4 cancri del terzo medio ridotti a pT0N0; 36 tumori ridottisi dopo la terapia ma con evidenza di malattia residua (8 terzo medio; 28 terzo inferiore)]; l'Amputazione Ad domino-Perineale (APR) è stata eseguita in 12 casi (23%) (7 no responders, 1 pT0N0 terzo inferiore, 4 terzo inferiore con evidenza di downstaging ma con malattia residua).

Conclusioni: La Preop R±CT consente di ottenere un downstaging significativo tanto da permettere la salvezza degli sfinteri, senza compromettere i risultati oncologici.

Parole chiave: Carcinoma del retto, radio-chemio terapia preoperatoria, chirurgia conservativa sfinteriale.

ERUS is a good technique to evaluate tumor invasion depth, with an accuracy between 75 and 94%, but this accuracy decreases to 47-58%, for T2 and T3 tumors and in detecting tumor invasion after RCT. Endorectal MRI use is strongly restricted(3), and only the PET scan is reported to have a high sensibility: this procedure uses the FDG, a radioactive glucose metabolism marker for neoplastic cells, and could detect a local recurrence, so excluding the presence of fibrous tissue, and thus allowing a correct selection for sphincter saving surgery. At present, however, DRE is the most effective criteria in surgical choice, since some malignant cells, responsible for late local recurrences, can be still detected in the scar. The goal of this review is to verify the effectiveness of preoperative R±CT in rectal cancer, on locally advanced rectal cancer, in order to evaluate the downstaging and the possibility to perform sphincter saving surgery in the most of patients.

## Materials and Methods

In the period 1985-2000, 392 patients with rectal cancer within 15 cm from anal verge were examined. Mean age was 63 years (range 32-90). Twenty patients (5.1%) with A stage tumor were excluded such as 75 (19.1%) with locally advanced cancer and distant metastases; 297 patients observed were divided as follows: 125 patients (42%) with upper third tumor, 74 (25%) middle third; 98 (33%) lower third. Of 172 patients (58%) with a middle-lower third tumor, 52 underwent a preoperative R±CT

[14 patients middle third (73%), 38 lower third (17%)]. Sex ratio F/M was 0.5. In this group of 52 patients, tumor stage, determined by Digital Rectal Examination (DRE) and ERUS, was as follows: 44 patients (86.4%) presented T3 stage tumor, 8 patients (15.4) a T4 mass. Thirty-two patients underwent RT alone, 20 a combined treatment. Mean age of this group was 57 years (range 42-67). Patients received 45 Gy for 5 weeks in 25 fractions, together with continuous administration of 5-FU (300-500 mg/m<sup>2</sup>/die). Some of the lowest lesions received an extra perineal dose of radiations (500 rads). Surgical operation was performed in this group 6 weeks after the treatment ± 7 days. Mean follow-up was 48 months (range 27-69).

## Results

All patients of neoadjuvant combined treatment group accomplished the therapy. They also underwent a post-operative RCT. In two cases, a systemic toxicity related to neoadjuvant therapy is reported with a subsequent treatment temporary suspension. Downstaging of T3-T4 tumors, at least of 1 T-stage level, was detected in 45 patients (86%) (8 middle third; 32 lower third); in 5 patients (9.6%) (4 middle third, 1 lower third), tumor stage decreased to pT0N0, while in 7 (13.5%) (2 middle third, 5 lower third), there was no response. All patients underwent a potentially curative surgical treatment, including a Total Mesorectal Excision (TME). Surgery was performed 6 weeks ±7 days after the therapy. An Anterior Resection (AR) was performed in 40 patients of this group (77%) [4 Downstaged to pT0N0 middle third cancers; 36 downstaged but with residual disease (8 middle third, 28 lower third)]; APR was performed in 12 (23%) (7 No responders patients, 1 Downstaged to pT0N0 lower third cancer, 4 downstaged but with residual disease of lower third).

## Discussion

A correct evaluation of R±CT role in management of colorectal cancer must consider two main targets: the radicality treatment and of the decrease LR incidence. It is essential that patients enrolled in the study have a long follow-up period since LR in preop and postoperative irradiated patients appears later (40-42 months) than in normal patients in which it happens within two years after surgical treatment. Irradiated patients must be followed along a period of 5 years at least, since a delay in LR detection is reported.

A TME alone is reported to be as effective in reducing recurrences as a complimentary treatment, but this evidence is related to highly selected patients in which the total amount of rads and the interval before surgery appears to be inadequate. A 45 Gy dose is reported to

Table I – PRE-IRRADIATION CLINICAL T-STAGE COMPARED TO POSTOPERATIVE PATHOLOGICAL STAGE (PT)

Pre-irradiation T Stage		pT0	pT1	pT2	pT3	pT4
T3	44 (86.4%)	4	11	22	7	0
T4	8 (13.6%)	1	0	2	5	0
Total Nr	52 (100%)	5	11	24	12	0

be more effective than 27 or 35 Gy as a free interval of 6 weeks allows a significant downstaging (4), useful in sphincters saving treatment.

Preoperative R±CT can permit to recover sphincters without an impaired function nor a suture delayed healing (5). A 8 mm distance from the tumor can be considered safe since it has been reported that a distance less than 1 cm cannot modify treatment radicality (2). A preoperative combined treatment is followed in 60-70% of cases by a significant downstaging with a subsequent tumor disappearing in 8-35% of cases.

In our experience a downstaging was observed in 86.6% of patients, whereas a complete tumor disappearing is evaluated to be about 9.6% of patients. This great variability in results is due to the accuracy in detecting tumor cells in the tissue, to the gross size of the tumor and finally to the interval between the preoperative and the surgical treatment. A tumor mass >5cm and a free interval <4 weeks are reported as criteria to offer poor results. It is still debated how to select responders: p53 alterations absence in bioptic specimens could be somehow predictive of the outcome (6), such as FDG-PET could be helpful in distinguish a LR from a scar tissue.

Planning a correct surgical strategy after a combined preoperative treatment is crucial. In pT0 N0 and pT1-pT2 derived from an initial T3 tumor a choice between local excision or a regular resection is frequent (6, 7).

The opportunity of a tumor excision even if performed by TEM after a downstaging for combined treatment is still discussed (9, 11). Some Authors report a 6-15% of metastatic nodes in T1 tumors increasing in T2 and moreover a chance of detecting these nodes out of radiation fields: moreover no data are still available about the effects of R±CT on affected nodes.

Surgery is thought essential to date and treatment radicality is related to the tactile perception of a healthy margin resection: in 25% of cases malignant cells are still present in the mesorectum or in rectal wall even if the lesion disappeared from the mucosa.

Thus some Authors avoid a sphincter saving treatment if a scare tissue is handled.

A combined RCT is useful after a local transanal excision or TEM for tumors within 5-6 cm. If the depth or the margin are suboptimal and tumor grade is aggressive (9, 10, 11). Similar results are reported after APR and incomplete excision associated with an adjuvant or neo-adjuvant treatment. In our experience the percent of

performed APR raises from 23% in treated patients to 40% in patients with surgery alone (2, 11). On the contrary, sphincter saving procedures were performed in about 80% of treated patients with middle-lower third tumor.

Finally, the peroperative mortality is significantly lower (=0) in treated group since a protective colostomy is always performed, if compared with non-treated patients group where surgical options are different.

### Conclusions

In comparing different experiences three factors seem to be fundamental in order to plan a combined R±CT and a subsequent sphincter saving treatment: a) get a downstaging, b) consider the residual tumor mass; c) evaluate the mobility of the lesion (12).

In our experience R±CT allowed to perform conservative treatment of sphincteric function achieving a good oncological radicality.

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