

The rational principles of neo-adjuvant therapy for rectal cancer

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Abstract. *Background:* Aim of the study is to analyze rational principles which at present govern the neoadjuvant therapy for rectal cancer and justify his application. First step is definition of targets: cellular replication block, volumetric reduction of rectal cancer, mesorectum and lateral nodes (Down staging), reduction of side-effects on close organs, radiation on more limited tissue volumes, major series of sphincter saving procedures, minor risk of microscopic tumour deposits. Second step regards standards which Protocols strive in order to: patients selection, therapeutic index, restaging before surgery, total mesorectal excision (TME). Further step accounts for evidence of drawbacks, related to Neoadjuvant approach, both Radiotherapy alone (RT) or Radiochemotherapy (CH-RT). *Methods:* Indications for neoadjuvant therapy, basing a difference between the absolute and relative one, are explained. Given that granting role to such therapy still now remain partially unclear, we have outlined the following topics: A) survey of main protocols is managed, taking care on dose/response ratio, focusing on enhanced supply for fixed tumours, checking on a list of several drugs (oxaliplatinum, capecitabin, raltitrexed, CPT-11, eniluracil), which are medicated with RT and furthermore on a list of substitute RT methods (HART, IORT, Endocavitary). B) following whole treatments, according such a different approaches, analysis of obtained outcomes in the literature are carried out. C) Personal experience, basing on a previous series where Down-staging has been sought, comparing indicatively clinical and diagnostic data before neoadjuvant therapy and before surgery. D) List of open issues, not solved at present, is shown *Conclusions:* Neoadjuvant therapy may be considered a rational approach for treatment of curative rectal cancer; indeed, preliminary results seem to introduce a real advantage compared to adjuvant therapy, even if is mandatory to associate proper surgical procedure, as TME, to warrant low local recurrences. Targets, related to such therapy, may be noticed ideal even though outcomes don't come up always to statements. So, continuous efforts to ameliorate rates of free-disease series, as well mortality rates and toxical effects are advised.

Key words: Rectal cancer, neo-adjuvant therapy, targets of procedure

Introduction

The extra peritoneal rectal cancers are usually at risk of local recurrence (LR) after Surgery, thus enhanced when cancer is located in the third lower of rectum; the T3 or T4 and N1 Tumours are obviously at major risk than the less spreading ones.

The outcome of Rectal Surgery depends also on Surgeon expertise.

Indeed, ongoing treatments of low rectal cancers, variability between surgeons should be always considered because a number of studies has confirmed varying in LR rates (0-21%), in number of sphincter saving procedures and in morbidity rates (1).

Increased number of colo-rectal surgeons has shown improved outcomes, evidencing that “the surgeon” has to be listed as a “risk-factor”(2)

This assumption depends on a correct technical approach, such as described since 1982 by Heald (3): he focused major attention on surgical method regarding radical excision of meso-rectum (TME), performed in the appropriate plane, avoiding the endopelvic sheath; the percentages a better outcome in terms of LR rates were achieved, compared to series whose TME was not performed (2.4% vs. 8.2)

Finally, to still improve surgical outcomes a further effort to was made, since twenty years to now, by employing adjuvant therapies - Radiotherapy (RT) and Chemotherapy (CT) - resulting in significant reduction of local recurrence rates, however partially improving mortality but exposing patients to high morbidity.

Later on, a continuous change of adjuvant approach has been developed: in short, adjuvant therapy has been replaced, step by step, by neo-adjuvant approach.

Aim of our study is to focus the rational principles which, at present, may justify use of neoadjuvant therapies; a survey of literature data and analysis of related problems, resulting in there application, are emphasized.

Background

The neoadjuvant therapy purposes the following targets:

- Cellular replication block, temporary or steady, drawing condition that tissues are well oxygenated and so more sensitive to RT.
- Radiation on more limited tissue volumes compared to living volumes ongoing post-operative Radiotherapy.
- Volumetric reduction of neoplasia, mesorectum and lateral pelvic nodes.
- Minor risk of microscopic tumour deposits, minor risk of seeding, due to surgical handling.
- Reduction of side-effects on close organs, mainly on small bowel, which are not displaced in to the pelvis by post-operative adhesions.

- Faculty to perform a major series of sphincter saving procedures.

Those theoretical assumptions, which strongly had inspired the promoters of such methods, were turned out on drawing up proper protocols.

The protocols provide:

- 1) patients selection according to the most proper staging;
- 2) the Optimization of therapeutic index;
- 3) restaging before undergoing surgery;
- 4) total mesorectal excision (TME), owing to obtain the better curative surgery.

Besides the mentioned advantages we have taken in to account evident drawbacks:

1. Delay of Surgery.
2. Increase of Morbidity and actinic complications (bowel, genitor-urinary tract, skin).
3. Staging modification.
4. Risk of sterilization in young women.
5. Tumour growth ongoing RT.

Methods

Which are the indications of the neoadjuvant therapy?

Since staging was assessed according TNM classification, we think it's mandatory the separation between absolute and the relative one.

The former includes extraperitoneal rectal tumour, spreading deep layers in different degree (T3, T4), showing augmented nodes (N1); the latter includes the same tumours, spreading instead on muscular surface layer (T2), more extended than cm 3 (4-6)

As regards the optimization of therapeutic index the engaged way is only working in progress, in order to the difficult balance in evaluating drug action, rate of induced toxicity, percentages of significant downstaging, timing of follow-up and of several factors influencing LR.

The granting role of RT remains still now unclear; so, we have focused the following aspects:

- a) *Survey of protocols;*
- b) *obtained Outcomes through the used Methodologies;*
- c) *personal Experience;*

d) List of debated issues, still now opened, due to limits and advantages of diagnosis and care in rectal cancer.

Survey of Protocols

The fashions of RT realization have followed two main schools of thought: the French one, belonging to the G. Roussi Institute, the latter Swedish, which, first, have taken credit for organizing a multicentric liaison, intent to work in synergy, to collect a sharp increase of series.

Both schools carried out the "long-term" RT, split on 4-5 weeks, to achieve a whole dose, ranging from 40 to 55 Gy, followed by surgery, at the earliest 4-6 weeks from the end of RT (7-8).

The Swedish school encouraged too the "short term" RT, high dose (5 Gy split a day for 5 days, to achieve a whole dose of 25 Gy), followed by surgery, not later than a week (9).

Concerning guide-lines about extent of whole supply, the dose/response ratio has to be noticed worthwhile, further to retrospective studies which have outlined the following points:

- Provided that RT is supplied as "short term" (25-30 Gy), the whole dose decreases local relapses incidence, prolongs too the disease free time from relapses, so long as to double it.
- In case of higher doses, more than 40 Gy, currently split from 150 to 200 cGy a week, the effect results in full clearout of outer tumour deposits.
- More high doses, still 55 Gy, are advised for "adverse" tumours, in terms of fixity, spread and location, less than 6 cm from ano-rectal junction.

Both the neoadjuvant approaches purposed to check different goals, according the aforementioned conditions; indeed, by the "long term" RT the target to achieve a volumetric reduction of neoplasm and a clearout of metastatic nodes was obviously evident; furthermore, given the protocol which delayed surgery 4-6 weeks thereafter, enhancement of cyto-reductive effects was verified throughout this interval.

Concerning "the short term" RT, the target was referred to cellular replication block, making no pre-

tence to volumetric reduction; moreover, shortcomings due to delay of surgery and related psychological ill effects, as in "long term" RT, were avoided by the choice of "short term" RT.

Further improvements which took advantage of neoadjuvant RT protocols were gained by a better supply of radiate dose (for instance: by the opposite bundles) resulting in lower side effects; however the main revelation regards association RT-CH; RT effects were hot up, purposing to preserve patient from tumour growth in case of short or no response to RT; indeed, ongoing RT kinetic cellular studies has proven and quantified risk of neoplastic proliferation, showing that average potential doubling time (Tpot) lies in 3.9 days; so, associated RT-CH may be considered as an "accelerated" treatment because the cyclo-specific drug is at once supplied to wipe-out selectively spreading cells (10).

At present we are watching to continuous new compounds between more chemotherapeutic drugs and RT; aim is to hopefully achieve better outcomes according the "space cooperation" that is both local control by RT and systemic control of micrometastasis by CH.

A list of new drugs includes eniluracil, oxaliplatin, capecitabin, raltitrexed, CPT-11: drug supply may be combined to short or long term RT.

Phase I - II studies are still ongoing, so advantages will be to prove with regard to 5-FU alone or 5-FU together with leucovorin, as well by bolus, as by continuous infusion.

Further RT procedures cover:

- High accelerated RT (HART): the method includes to draw in weeks of treatment (2.5), to supply a whole dose of 41 Gy (1.6 Gy one day split), to suddenly perform surgery at the end of RT (11). Nevertheless, the theoretical advantages were not proven, so the method is not becoming widespread.
- Intraoperative RT (IORT): the method takes advantage to supply Rt ongoing operation (range 15-20 Gy) by direct boost on tumour, avoiding to radiate the close small bowel (12, 13); thereafter, adjuvant therapy needs to be carry out. Elective indication includes extended and fixed tumours. Main shortcoming which has

strongly limited the IORT enforcement depends on logistic difficulty to move patients on-going surgery.

- Endocavitary RT, Brachithery; the method was initiated by the French school (4), regarding small (within cm 3) or mobile lesions, classified as T1; sometimes it was associated to external RT.

Obtained Outcomes through the used methodologies

Positive results have been achieved on the local recurrences in the randomized trials through the only preoperative radiotherapy: the local control results significantly better in 8 on 15 studies and quantifiable between 80% and 91%. The decrease of the LR is on average about of 15% with respect to 30% observed before of the use of the RT (14).

Further improvement in the resectable tumours has been obtained by using the technique of the Total Mesorectal Excision (TME) associated to RT. As regards this technique, an important dutch multicentric trial performed on 1861 patients (15) demonstrated that the combination of TME with short-RT reduces the local recurrences until 2.4% with respect to 8.2% obtained in the controls underwent the only TME. Two very important information have been obtained by this study, about the evidence that no significant decrease of LR was observed in patients with tumours which are distant more of 10 cm from the anal verge and with tumours in I or IV stadium according to TNM classification.

However, a higher survival does not correspond at the improvement of the local control; an improvement has been shown in only 4 studies (7, 9, 16, 34) (Table 1), and the greatest difference as regard the survival has been obtained only in one study: 58% vs.48% (7).

The toxicity due to RT treatment has been limited; in two studies, the major toxicity has been reported during the treatment (16), nevertheless, this did not prejudice the surgical procedure.

It is to report that the surgical mortality has been mainly showed in some studies in which a short-term RT has been used, with respect to only surgical treatment (17, 18), even if an obsolete technique such as that at opposite bundles was chosen.

Table 1. Results of trials comparing surgery vs. neoadjuvant therapy

	Surgery	Rt+Surgery
Stockolm II Trial (S) (1996) (9)	56%	62%
Swedish Trial (S) (1997) (7)	48%	58%
EORTC (L) (1988)	49%	52%
MRCRCWP (L) (1996) (16)	46%	52%

(RT alone; S: Short Term; L: Long term)

EORTC studies report a higher morbidity due to early complications after short RT in 44% of patients vs 34% treated only with surgery and, after long RT in 41% vs 28%.

The most number of early complications such as perineal infections, delayed cicatrisation, and altered function of anastomoses have been found in randomized studies (19, 20) and in recent observations (21).

Some randomized studies performed during the last 10 years mainly in North American countries, have clarified the advantages of the neoadjuvant radio-chemo-therapy with respect to adjuvant and demonstrated a local control of the pathology between 83% and 92%.

EORTC study (22), which has compared the neoadjuvant radio-chemo-therapy with the only RT treatment, has showed the same rate of recurrences (15%), but a significantly better survival at 5 years in the group underwent radio-chemo-therapy with respect to that treated with only RT (59% vs 46%).

Moreover, these studies demonstrate a relationship between Down-staging and disease free and global survival. TNM stadium is inversely related with the local control (23-25). The analysis of the two different modalities of neoadjuvant therapy, as regards the total pathological remissions (TPR), shows a higher percentage of TPR in patients treated with radio-chemo-therapy than that obtained using only RT. This treatment is able to induce about 5-10% of TPR, whereas the simultaneous use of 5-FU, according to the various procedures of administration, let us to obtain TPR in 20-25% of cases (or can increase TPR until 20-25% of cases). Further therapeutic option is the adjuvant chemo-therapy after pre-operative radio-chemo-therapy; this procedure seems favourable also for patients with pN0 post-operative stadium (26).

Considering these data, further studies are started to identify clinical and biological factors which can predict the tumour answer (27, 28) and the pelvic recurrences (29).

At present, molecular biology factors do not seem to be predictive in order to extent of only preliminary reports (30), instead histo-pathological findings, as circumferential margin involvement, may play a definite role (31-35).

Personal experience

The application of neoadjuvant therapy in rectal cancer need a survey of diagnostic procedures in order, as mentioned, to repeat restaging, before surgery; moreover may be useful to quantify, even indicatively, the achieved down-staging and to try some correlation with outcomes of treated patients.

The diagnostic schema for restaging, is reported in table 2.

Methods of down-staging evaluation are shown in table 3.

In table 4 we exhibit the adopted layout for patients, treated in our Unit: in order to reduce toxic effects CH is only supplied on first and last week.

Furthermore, we have treated preoperatively with RT alone in the past (from November 1997 to may 2000) a small series of 21 patients with a total of 62 rectal tumours, whose characterises were:

Age ranged from 49 to 88 years, men/women ratio 9/12.

Table 2. Diagnostic schema for restaging

- Clinical examination , Endoscopy
- Pelvic, abdomen TC or MRI (comparable with previous scan)
- Endosonography (comparable)

Table 3. Methods of down-staging evaluation

- Pooling of whole data
- Matching of both data, before Neoadjuvant, before surgery
- Assessment of down-staging, outlining indicatively percentages of tumour volumetric reduction: > 50%, 30-40%, 20-30%, <10%.
- Survey of surgical procedures related to achieved down-staging

Table 4. Adopted layout for Neoadjuvant Therapy

Day	1	8	15	22	30-40 (post end RT- CH)
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-- = Rt 180 cGy/die, 1, 2, 3, 4, 5 gg (I, II, III, IV week)

^ = 5-FU 1 gr/MQ/die, 1, 2, 3, 4, 5 gg (I, IV week)

ø = Oxaliplatinum 80 mg/MQ 1 gg. (I, IV week)

* = Surgery

Tumours were detectable nearby anal verge in a range from 2 to 10 cm.

The caudal-cranial extension was getting on cm 3 in whole series.

The linear-circumferential extension was shown in 11, out 21 cases.

The tumour fixity was detectable in 12, out 21.

In this series we have checked percentages of Down-staging, according the mentioned criteria. Results are shown in table 5.

The higher percentage of reduction correlates the more conservative procedure; in detail, the percentage of sphincter saving procedures was 66% (14/21); 6 out of 7, cases whose Miles procedure was performed, showed a low down-staging; furthermore 2 cases, whose pTNM has shown Tx, belonged to cases who-

Table 5. Indicatively achieved percentages of down-staging

% Down-staging	Cases	Operation	pTNM
> 50	3	Colo-Anal Res. (2)	T3N0G2 TXN3G4
		Anterior Res.	TXN0G2
30-40	5	Anterior Res. (2)	T3N0G2 T3N1G3
		Colo-Anal Res.	T2N0G2
		A.A.R (Miles)	T2N0G3
		T. Anal Excision	T2NXG3
20-30	8	(6) Anterior Res.	(3)T3N0G2 (3)T3N1G3
		(2) A.A.R (Miles)	T3N0G2 T3N2G3
< 10	5	Anterior Res.	T3N1G2
		(4) A.A.P (Miles)	(2)T3N1G3 T3N1G2 T3N0G2

se resulted in higher reduction percentage. LR was observed in 2 cases. In our series any data concerning survival 5 years free disease are yet not available;

Those data align themselves according literature data in which we discover that RT reduce pathologic staging even if exists a real risk to underestimate tumours with bad outlook; moreover, the expected outcomes include 15% of sterilized tumours, 40% of significant down-staging, in detail the number of positive nodes will be reduced from 42% to 33% (32).

List regarding open question

In rectal cancer enforcement of neoadjuvant therapy opens the following issues:

- 1) preoperative stand in differing topographically between intraperitoneal and extraperitoneal rectum;
- 2) difficulty of proper preoperative staging, both in onset and in restaging;
- 3) how to evaluate the down-staging effectiveness?
- 4) how to predict both toxicity and mortality related to neoadjuvant therapy?
- 5) How much neoadjuvant therapies are still timely when trans mesorectal excision (TME) is associated?
- 6) Difficulty in quantifying age-related sphincter damage ongoing sphincter saving procedures as low anterior resection or colo-anal resection.
- 7) Which long term side effects, RT-CH related?

Conclusions

The mentioned analysis on neoadjuvant therapy has been performed to highlight a real description on both advantages and limits in treating rectal cancer.

First it's evident that at present this approach is wide-spread, even if partially accepted.

Preliminary results seem to introduce a real advantage of neoadjuvant therapy, compared to the adjuvant one, even if is mandatory to associate proper surgical procedure, as TME, to maintain low LR.

Furthermore, standard methods are yet not admissible in order a lack of guidelines (33) and onset of

different protocols, both for RT alone or CH-RT associated, indicates a continuous effort to ameliorate rates of free-disease series, as well mortality rates and toxic effects.

Indeed, never procedure is faultless, so, in avoiding adverse side effects whose patients often complain, we could merely throw on results of multicentric trials, managed on wide series, throughout long term follow-up.

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