Present indications for adjuvant therapy in resectable rectal cancer



B.D. MINSKY

Vice Chairman and Member Department of Radiation Oncology Memorial Sloan Kettering Cancer Center Professor of Radiation Oncology Cornell University Medical College - Ittaca, N.Y. 14853

Introduction

Combined modality therapy is effective adjuvant therapy for many patients with clinically resectable rectal cancer. The indications for adjuvant therapy for rectal cancer are based on the patterns of failure after surgery. Despite radical surgery, local-regional failure occurs frequently in patients with transmural or node-positive rectal cancers. The incidence of treatment failure in the pelvis is directly related to the extent of transmural penetration (microscopic vs. gross) and the additive risks of lymph node metastases. In the post-operative setting it use is dictated by pathologic stage and the type of operation (i.e. conventional surgery or a local excision). In the preoperative setting it depends on clinical stage and the need for sphincter preservation. This review will examine both the selection criteria and results of adjuvant combined modality therapy for patients with clinically resectable rectal cancer.

Post-operative adjuvant therapy following conventional surgery

Selection Criteria

Most patients in United States undergo surgery and, if needed, receive post-operative adjuvant therapy. The primary advantage with this approach is pathologic staging.

Abstract

Combined modality therapy is an effective adjuvant therapy for many patients with clinically resectable rectal cancer. The indications for adjuvant therapy for rectal cancer are based on the pattern of failure after surgery. Despite radi -cal surgery, local-regional failure frequently occurs in patients with transmural or node-positive rectal cancers. The inci dence of treatment failure in the pelvis is directly correla-ted with the extent of transmural penetration (microscopic vs gross) and the additional risk of lymph node metastases. In the post-operative setting its use is dictated by patholo -gic stage and the type of operation (i.e. conventional sur -gery or a local excision). The choice of which post-operati ve adjuvant regimen to recommend in the non-protocol set ting remains controversial. If 5-FU alone is used, then it is best administered by continuous infusion. In the preope rative setting, the use of adjuvant therapy depends on the clinical stage and the need for sphincter preservation. Phase I/II trials examining the use of newer chemotherapeutic agents such as Tomudex, ŬFT/leucovorin, CPT-11, oxaliplatin, eni luracil and capecitabine with preoperative radiation therapy are in progress. This review examines both the selection cri teria and results of adjuvant combined modality therapy for patients with clinically resectable rectal cancer. Key words: Rectal neoplasms, drug therapy, radiotherapy, surgery, treatment outcome, adjuvant.

Abstract

ATTUALI INDICAZIONI AL TRATTAMENTO ADIU -VANTE DEL CARCINOMA RESECABILE DEL RETTO

Molti pazienti con carcinoma resecabile del retto possono giovarsi di terapie adiuvanti integrate. Le indicazioni a tali trattamenti si basano sul pattern delle riprese di malattia dopo resezione chirurgica. Infatti, nei pazienti con carci noma che supera la parete del viscere, o con interessamen to linfonodale, l'incidenza di recidive loco-regionali è rela tivamente elevata anche dopo chirurgia radicale. Il tasso di recidive pelviche, in particolare è direttamente correlato all'estensione e dal grado di penetrazione attraverso la pare te rettale (microscopica versus macroscopica), con un rischio aggiuntivo per le metastasi linfonodali.

Nella fase post-operatoria, l'indicazione al trattamento posto peratorio dipende dallo stadio patologico e dal tipo d'inter vento (ad esempio: resezione tradizionale o escissione loca -

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le). La scelta del trattamento adiuvante ottimale, al di fuori degli studi clinici, resta tuttavia ancora discussa. Nel caso di somministrazione concomitante del solo 5 Fluorouracile, è evidente il vantaggio derivante dalla somministrazione per infusione continua. Nella fase pre-operatoria, l'uso della terapia adiuvante è indicato sulla base dello stadio clinico e dal tentativo di preservare la funzione dello sfintere ana le. Attualmente sono in corso una serie di studi clinici di fase I/II, volti a valutare nuovi farmaci da utilizzare in associazione alla radioterapia, quali: Tomudex, UFT/ Leucovorin, CPT-11, oxaliplatino, eniluracile e capecitabina.

In questa revisione vengono esaminati sia i criteri di sele zione che i risultati del trattamento adiuvante integrato nei pazienti con carcinoma rettale resecabile.

Parole chiave: Neoplasie del retto, chemioterapia, radioterapia, chirurgia, adiuvante, risultati della terapia.

Despite advances in pre-operative imaging techniques which allow more accurate patient selection, post-operative therapy remains the most common approach. The primary disadvantages include an increased amount of small bowel in the radiation field (1), a potentially hypoxic post-surgical bed, and if the patient has undergone an APR, the radiation field must be extended to include the perineal scar.

Based on a compilation of selected series, the incidence of local failure (as a component of failure) is less than 10% in stages $T_{1-2}N_0M_{0i}$ increasing to 15% to 35% in stages $T_3N_0M_0$ and $T_1N_1M_0$, and as high as 45% to 65% in stages $T_{3-4}N_{1-2}M_0$ (2). When local failure does occur it is severely debilitating and salvage has been of limited success. Therefore, decreasing local failure is, by itself, an important endpoint in the treatment of rectal cancer.

Some physicians contend that adjuvant therapy is not necessary if patients undergo resection with a total mesorectal excision. In one series, total mesorectal excision, which involves sharp dissection around the integral mesentery of the hind gut, decreased the local recurrence rate to 5% (3). These data must be interpreted with caution for a number of reasons. First is selection bias. This operation allows the identification and exclusion of patients with more advanced disease as compared with patients treated in the adjuvant trials in which more conventional surgery is performed. Second, some patients with T_3 and/or N_{1-2} disease received radiation therapy with or without chemotherapy (i.e. 18% in the series by Haas-Kock et al, (4) 28% in the series from Enker and associates (5), and 58% in the series from Arenas et al. (6) In a combined analysis of 1411 patients from 5 international centers, an undisclosed number received adjuvant radiation or combined modality therapy (7). Third, some series (i.e. Aitken et al) exclude operative deaths (8). Lastly, total mesorectal excision may also be asso-

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ciated with higher complication rates. In the Basingstoke Hospital experience reported by Carlsen and colleagues, the anastomotic leak rate was 16% in patients who underwent total mesorectal excision (all who required hospitalization) compared with a leak rate of 8% in a similar group of patients who underwent conventional surgery (with only 25% requiring hospitalization) (9). Poon and colleagues recommend the creation of a defunctioning stoma to decrease the high leak rate with total mesorectal excision (10).

There are retrospective data which suggest that there may be subsets of patients with T_3N_0 disease who may not require adjuvant therapy as well as patients with Stage I disease who should be considered for adjuvant therapy (11, 12). In a review of 117 patients with T_3N_0 disease, Willett et al identified a favorable subset of patients with well or moderately differentiated cancers invading less than 2 mm into the perirectal fat who, following surgery alone, had a 10-year actuarial local failure rate of only 5% compared with 29% in T₃N₀ patients without those favorable features (12). In a separate analysis he identified a subset of patients with Stage I disease who have an increased incidence of local failure following an APR (13). These results need to be confirmed in a randomized trial before a change in the standard of care of combined modality therapy can be recommended.

Results

Following the publication of the randomized trials from the GITSG (14) and Mayo/NCCTG (79-47-51) (15) which revealed a significant improvement in local control (Mayo/NCCTG) and survival (GITSG and Mayo/NCCTG) with post-operative radiation plus bolus 5-FU/MeCCNU, the National Cancer Institute Consenus Conference concluded in 1990 that combined modality therapy was the standard post-operative adjuvant treatment for patients with T₃ and/or N₁₋₂ disease (16). As seen in Tab. I, although radiation therapy decreases local recurrence in half it is the addition of 5-FU based chemotherapy which further decreases local recurrence to

Tab. I – T3 AND/OR N1-2 RECTAL CANCER RESULTS WITH POST-OPERATIVE COMBINED MODALITY THE-RAPY

Series	% Local Failure	Survival		
GITSG 7175 (14)	11	54% 8-Yr		
Mayo/NCCTG				
79-47-51 (15)	14	53% 5-Yr		
86-47-51 (79)	9-11	60-70% 4-Yr		
INT 0114 (80)	9-13	78-80% 3-Yr		
NSABP R-02 (81)	8	62-65% 5-Yr		

approximately 10% and is the agent responsible for increasing overall 5-year survival by approximately 10-15% (from 50% up to 60-65%).

Building on the positive results of continuous infusion 5-FU reported in the Mayo/NCCTG 86-47-51 trial, the replacement post-operative Intergroup trial INT 0144 was designed. The primary endpoint of this trial is to determine whether there is a benefit of continuous infusion 5-FU throughout the entire chemotherapy course (6 cycles) as compared with continuous infusion only during the combined modality segment (2 cycles) and bolus 5-FU during the remaining 4 cycles. The control arm is arm 4 (bolus 5-FU/Leucovorin/Levamisole) of INT 0114. The trial opened to accrual in 1993 and completed accrual in 2000.

The choice of which post-operative adjuvant regimen to recommend in the non-protocol setting remains controversial. If 5-FU alone is used then it is best administered by continuous infusion. Otherwise the published 5-FU based regimens probably have equal efficacy and the choice of a regimen should be based on factors such as their acute toxicity profiles and patient compliance.

Post-operative adjuvant therapy following a local excision

Selection Criteria

An alternative method of treating rectal cancer is a local excision followed by post-operative adjuvant therapy. In order to determine which tumors have a high enough incidence of local failure or positive mesorectal and/or pelvic lymph nodes to require adjuvant pelvic radiation, it first must be determined which tumors are adequately treated with local therapy alone. The selection of tumors for local therapy is based on both clinical and pathologic factors. Clinical information such as tumor size, mobility, location, and circumference can be obtained at the time of physical examination. Accurate pathologic information is more difficult to obtain from a biopsy. Of the available local therapies, only a full thickness local excision provides accurate pathologic information.

A major limitation of the series which examine local excision alone is that the analyses are univariate rather than multivariate. Therefore, clinical and pathological factors are not examined as independent variables. Further, there is variation in patient selection, the definition of clinical and pathological features, and the length of follow-up among the series. Due to these differences, it is difficult to make firm recommendations for the selection of patients for conservative management based solely on clinical criteria. The most reasonable approach is if a local excision can be performed adequately (i.e. full thickness, non-fragmented, and with

negative margins) then the clinical criteria for a local excision have been met.

Pathologic criteria are more objective. Patients with T1 tumors without adverse pathologic factors have a low enough incidence of local failure (5-10%) and positive nodes (<10%) that they do not require adjuvant therapy. However, once adverse pathologic factors are present (high grade, BVI, LVI, colloid histology, signet-ring cell) (17-19), or the tumor invades into or through the muscularis propria (18, 20, 21), the local failure rate is at least 17% and the incidence of positive mesorectal and/or pelvic nodes is at least 10-15% (17). Biggers et al reported the results of 141 patients with T2 rectal cancers who underwent local excision alone at the Mayo Clinic (21). Blumberg and associates found positive nodes in 10% of T_1 and 17% of T_2 cancers (22). In the combined group of 159 patients the incidence increased with the presence of LVI (LVI-: 14% vs. LVI+: 33%). Even in the 42 patients with the most favorable characteristics (well or moderately differentiated, LVI-, T1 cancers, 7% had positive nodes. The 5-year survival was 65% and the local failure rate was 27%. Hager and colleagues performed a local excision on 20 patients with T2 rectal cancers which were otherwise "low risk" (nonmucinous, well-moderately differentiated, no LVI, and negative margins) (20). The incidence of local failure was still 17%. Other series have reported local failure rates as high as 43% in patients with T₂ cancers following either local excision or transanal excision (23).

Willett et al reported a group of 40 patients who underwent local excision alone at the Massachusetts General Hospital (MGH) (18). In this series, a separate analysis was performed of those patients whose tumors had unfavorable clinical and pathological factors. Factors including tumor size >3 cm, high grade, > T_2 , vascular invasion (BVI and/or LVI), moderate or marked stromal fibrosis, a fragmented resection, or positive margins and were associated with a local failure rate of at least 20% as well as an increase in distant metastasis. Therefore, local therapy alone is inadequate for tumors with these adverse pathologic factors.

Results

As seen in Tab. II, the 5-year actuarial survival in these selected series is approximately 80% (range: 70-94% (24-33). In most series, patients had T_{1-3} tumors and underwent a local excision followed in 4-6 weeks later by 45-50 Gy to the pelvis. Some patients received an external beam or brachytherapy boost. In most series, a limited number of patients received 5-FU. Although not randomized, these survival data appear comparable with the results of radical surgery alone for stage $T_{1-2}N_0$ disease.

The Intergroup CALGB 8984 trial is the only prospective, multi-institutional Phase II trial. Patients underwent a local excision with careful assessment of negative mar-

Tab.	II – LOCAL	EXCISION	PLUS	POST-OPERA	ATIVE	THERAPY:	SURVIVAL,	SALVAGE,	AND	FUNCTIONAL	RESULTS
					SE	ELECTED S	ERIES				

Series	#	% T3	% 5-FU	Survival	Function	Local Failures Salvaged With Apr
U Florida (24)	45	2	4	88% cause specific	_	1/5 salvaged
NE Deaconess (25)	48	10	54	94% crude	-	3 of 4 salvaged
MD Anderson (26)	46	33	17	_		All continent –
U Pennsylvania (27)	16	32	0	94% 3-Yr actuarial 77% 3-Yr colostomy free	92% satisfactory	2 of 2 salvaged
MGH (33)	47	0	55	74% 5-Yr Disease Free	_	Of 14 failures, 5/9 salvaged
Catholic University (31)	21	0	0	81% 5-Yr actuarial	100% good to ^A excellent	1 of 2 salvaged
Fox Chase (32)	21	19	10	77% 5-Yr actuarial	82% good to excellent	3 of 4 salvaged
CALGB (34)	51 ^B	0	100	85% 6-Yr actuarial	_	4 of 7 salvaged
Memorial (28) ged	39	21	51	70% 5-Yr actuarial	94% good to ^A excellent	Of 8 failures, 5 of 8 salva-
Sloan Kettering				87% colostomy free		
Vancouver (30)	23	9	0	81% 5-Yr disease free 77% cause specific	-	3 of 7 salvaged

A = Memorial Sloan Kettering Cancer Center Sphincter Function Scale

B = Analysis is limited to the 51 of 110 patients (all with T2 disease) who underwent a local excision and received post-operative radiation therapy + chemotherapy

gins and, depending on T stage, received post-operative combined modality therapy (34). A total of 110 eligible patients (all with negative margins) were entered. The 51 patients with T_2 disease received post-operative combined modality therapy. With a median follow-up of 48 months the crude local failure rate was 14% and the 6-year failure free survival was 71% and overall survival was 85%. This approach is feasible in a multiinstitutional, cooperative group setting.

When the series are combined, the average crude local failure rate increases with T stage: T_1 : 5%, T_2 : 14%, and T_3 : 22%. When the series are combined the crude incidence is 12% and increases with the percentage of T3 cancers included in each series.

In summary, the data suggest that the approach of local excision and post-operative radiation is a reasonable alternative to radical surgery in selected patients. It should be limited to patients with either T_2 tumors or T_1 tumors with adverse pathologic factors (poorly differentiated and/or LVI). Although the local failure rates are approximately double those reported with radical surgery, half of the failures can be salvaged with an APR without an apparent detriment to overall survival. Functional results are generally good to excellent. Transmural (T_3) tumors have a 25% local failure rate are treated more effectively with radical surgery and pre- or post-operative therapy. The results of local excision and post-operative radiation therapy are encouraging however, randomized trials are needed to determine if this approach ultimately has similar local control and survival rates as radical surgery.

Pre-operative adjuvant therapy

Selection Criteria

Pre-operative adjuvant therapy (most commonly radiation therapy combined with systemic chemotherapy) is an alternative to post-operative therapy (35-46). The primary advantages of pre-operative therapy are sphincter preservation and a lower incidence of acute toxicity.

The disadvantage of pre-operative radiation therapy is the potential of overtreating patients with either early (pathologic stage $T_{1-2}N_0$) or metastatic disease. With improved imaging techniques such as endorectal ultrasound (47), ultrasound guided pararectal lymph node biopsy (48), CT (49), MRI with a phased-array (50) or an endorectal coil (51), and positron emission tomography (52-54), the number of patients who are overtreated is decreased. Experienced investigators report the accuracy of endorectal ultrasound in predicting T stage pre-operatively as high as 90% (55, 56).

From the viewpoint of sphincter preservation, the advantage of pre-operative therapy is to decrease the volume of the primary tumor. When the tumor is located in close proximity to the dentate line, this decrease in tumor volume may allow the surgeon to perform a sphincter preserving procedure which would not otherwise be possible. However, patients whose tumors directly invade the anal sphincter are unlikely to undergo sphincter preservation even following a complete response.

Conventional doses and techniques of radiation are

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recommended. These include multiple field techniques to a total dose of 45-50.4 Gy at 1.8 Gy/fraction. Surgery should be performed 4-6 weeks following the completion of radiation. This design allows for the recovery from the acute side effects of radiation and enhances tumor downstaging.

Since the publication of the Swedish Rectal Cancer Trial which revealed a significant improvement in survival with intensive short course pre-operative radiation, some physicians have advocated this alternative approach (57). Typically the intensive short course includes 25 Gy in 5 fractions followed by surgery one week later. Not only are these treatment programs associated with increased surgical morbidity and mortality (58, 59), but virtue of their design, no not enhance sphincter preservation. Therefore, they should be used with great caution.

For patients with clinically resectable disease, the preoperative approach should be used in situations where at initial presentation, sphincter preserving surgery is not technically possible. The decision of whether to use preoperative radiation therapy or pre-operative combined modality therapy is based on the results of the transrectal ultrasound. If a transrectal ultrasound reveals T_2 disease the patient may have pathologic $T_2N_0M_0$ disease therefore, the sole reason for the pre-operative therapy is to convert the operation from an abdominoperineal resection to a low anterior resection/coloanal anastomosis. In this setting, pre-operative radiation therapy alone is recommended. If positive mesorectal and/or pelvic lymph nodes are identified at the time of surgery, the patient should receive 6 months of adjuvant post-operative 5FU based chemotherapy. There are two potential disadvantages to this approach. First, the ultrasound may understage approximately 10% of patients who have pathologic stage T_3 disease. Second, since pre-operative radiation downstages pelvic lymph nodes by approximately 50%, the true incidence of node positive disease is unknown and some node positive patients may not receive chemotherapy. Obviously, these disadvantages need to be weighed against the risk of overtreating these patients with combined modality therapy.

For patients with transrectal ultrasound stage T_3 disease, pre-operative combined modality therapy followed by surgery and post-operative 5-FU based chemotherapy is recommended. This approach is based on extrapolation of the significant improvement in local control and survival in patients with T_3 and/or N_{1-3} disease who receive adjuvant post-operative combined modality therapy (16). Whether pre-operative combined modality therapy is more effective than pre-operative radiation therapy is unknown. A ongoing randomized trial from the EORTC will address this question.

Clinical Experience with Sphincter Preservation

A total of 7 series have reported results in patients with clinically resectable, invasive rectal cancer ($T_{2'3}$ or T_4 tethered to the vagina) who underwent a prospective clinical assessment by their surgeon prior to the start of pre-operative therapy and were declared to need an APR (Tab. III). All use conventional radiation techniques and,

	Wagman (37) (MSKCC)	Grann (82) (MSKCC)	Rouanet (39) (Montpellier)	Hyams (40) (NSABP R-03)	Maghfoor (36) (Ellis Fischel)	Valentini (41) (Catholic Univ)	Francois (46) (Lyon R90-01)
# Enrolled	36	72	37	59	29	83	201
# Declared to Need							
an APR	36	31	37	22	29	47	343
# Who Underwent							
Surgery	35	31	27	22	29	81	34
# With T3 Disease	31 (86%)	31 (100%)	12 (32%)	22 (100%)	25 (86%)	83 (100%)	62%
# Underwent LAR							
± Coloanal	27 (77%)	31 (89%)	17 (63%) ¹	16 (23%)	22 (76%)	31 (66%)	15 (44%)
Anastomosis							
% Local Failure		17	2	8	NA	3	10 12
% Survival	64% 5-Yr	95% 3-Yr	83% 2-Yr	NA	87%2	72% 5-Yr	75% 3-Yr
# Evaluable for							
Sphincter Function							
Analysis	27 (77%)	26	14 (52%)	NA	NA	63	824
Sphincter Function	85% Good to Excellent	81% Good to Excellent	71% Perfect	NA	NA	6% moderate soilage	78% normal

Tab. III - RESULTS OF PRE-OPERATIVE THERAPY IN PATIENTS PROSPECTIVELY DECLARED TO REQUIRE AN APR

MSKCC = Memorial Sloan Kettering Cancer Center

NA = Data not reported in the manuscript

1 = 15% underwent a local excision therefore 78% had sphincter preservation

2 = Disease free survival with a median follow-up of 12 months

3 = Limited to the subset of 34 patients (out of a total of 201) randomized to either arm who were declared to need an APR.

4 = Includes all patients in the trial who underwent sphincter preservation

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with the exception of the R90-01 trial with used 3 Gy fractions, the remainder used standard radiation doses (1.8-2 Gy/fraction). Two of the series are from Memorial Sloan Kettering. The initial approach to sphincter preservation at Memorial Sloan Kettering was pre-operative radiation therapy alone and the results of this prospective Phase I/II trial have been reported by Wagman et al (37). The current approach at Memorial Sloan Kettering is pre-operative combined modality therapy and has been reported by Grann and associates (38). Pre-operative radiation therapy (without chemotherapy) was reported by Rouanet et al from the Montpellier Cancer Institute (39) and the R90-01 trial from Francois and associates from Lyon. The other 3 trials used combined modality therapy. Hyams and colleagues reported an interval analysis of the ongoing NSABP R-03 phase III randomized trial of pre-operative versus post-operative combined modality therapy (40). The remaining trials were reported by Maghfoor and colleagues from Ellis Fischel Cancer Center (36) and Valentini et al from the Catholic University in Rome (41).

Overall, 5 of the 7 trials suggest that, pre-operative therapy allows sphincter preservation in approximately 75% of patients judged clinically to require an APR. The majority have good to excellent functional results. Given the suggestion of decreased acute toxicity and enhanced sphincter preservation with pre-operative radiation therapy, 3 randomized trials of conventional dose pre-operative versus post-operative combined modality therapy for clinically resectable, T3 rectal cancer have been developed. Two are from the United States (INT 0147, NSABP R0-3) and one from Germany (CAO/ARO/AIO 94). All 3 use conventional doses and techniques of radiation therapy and concurrent 5-FU based chemotherapy as well as require a pre-operative clinical assessment declaring the type of operation required. Unfortunately, low accrual resulted in the early closure of the INT 0147 trial and the NSABP R-03 trials. The German trial continues to accrue patients and should help provide an answer to the relative effectiveness of pre-operative versus post-operative therapy and its ability to enhance sphincter preservation.

At the present time the most common preoperative combined modality therapy regimens include 45-50.4 Gy of pelvic radiation at 1.8 Gy/fraction plus concurrent bolus 5-FU/leucovorin (38, 60) or continuous infusion 5-FU (61, 62). Some have advocated 5-FU/mitomycin-c which is more commonly used in the treatment of anal cancer (41, 63). One trial using neoadjuvant 5-FU/methotrexate followed by continuous infusion 5-FU plus concurrent radiation did not report a benefit compared with conventional 5-FU/leucovorin (64). Phase I/II trials examining the use of newer chemotherapeutic agents (65) such as Tomudex (65-68), UFT/leucovorin (69, 70), CPT-11 (71, 73), oxaliplatin (74-76), eniluracil (77), and capecitabine (78) with preoperative radiation therapy are in progress.

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Autore corrispondente:

Bruce D. MINSKY, M.D.

Vice Chairman and Member Dep. of Radiation Oncology Memorial Sloan Kettering Cancer Center

Prof. of Radiation Oncology Cornell University Medical College

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