18 Applications in Rectal and Anal Cancer

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18.1 Rectal Cancer

18.1.1 Introduction

The rational for using combinations of radiation and systemic chemotherapy as a component of adjuvant treatment in stage T3/4 and/or node-positive rectal cancer (UICC stages II and III) is based on the risk of relapse after surgery alone and the evidence of radio- and drug-responsiveness derived from both laboratory studies and clinical trials. The past four decades have witnessed the development of a variety of preoperative and postoperative radio- and radiochemotherapy schedules designed to optimize the sequence of treatment modalities and the most appropriate scheduling of irradiation and 5-fluorouracil-based chemotherapy. Given that with optimized local treatment, including preoperative radiotherapy and total mesorectal excision (TME) surgery distant metastasis is by far the predominate pattern of tumor failure in rectal cancer presently, the future challenge is to integrate more effective systemic therapy into the multimodal concepts for this disease.

18.1.2 5-Fluorouracil-Based Radiochemotherapy

5-fluorouracil (5-FU), an analog of the pyrimidine uracil with a fluorine atom substituted in place of hydrogen at the carbon 5 (C-5) position, has been the most commonly used single chemotherapeutic agent for colorectal cancer during the past four decades, and will certainly also continue to be the backbone of modern drug combinations in the near future. Since its synthesis in 1957 by Heidelberger et al. (1957), the metabolism and mechanism of action of 5-FU have been studied in detail. 5-FU enters a complex anabolic process that accounts for cytotoxicity at the cellular level by interfering with normal DNA and RNA function. Heidelberger et al. (1958) also initially discov-

ered that the addition of 5-FU to radiation in rodent tumors markedly enhanced the effects of radiation therapy. Based on these early preclinical data, Moertel et al. (1969) administered 5-FU with radiation to patients with gastrointestinal cancers and noted significant activity. The pioneering contribution to the use of combined radiotherapy and FU was made by Byfield et al. (1982), who demonstrated that 5-FU radiosensitization resulted from specific time and concentration factors: The sensitizing effects of 5-FU in vitro are maximal when its exposure occurs for at least 24 h and up to 48 h after the radiation exposure, thus supporting a prolonged 5-FU exposure approach when given with fractionated irradiation.

18.1.2.1 Randomized Trials of Postoperative Concurrent RCT

Historically, the combination of postoperative radiotherapy and 5-FU-based chemotherapy has been shown in several randomized trials to reduce local recurrence rates and to improve overall survival compared with (conventional) surgery alone or surgery plus postoperative radiotherapy (Table 18.1). In the early GITSG 7175 trial, the best local control was achieved with combined RCT (local relapse rate of 11 vs 20% with RT alone), whereas no impact on local control was noted with chemotherapy as single adjuvant treatment (local relapse rate of 27 vs 24% with surgery alone; Gastrointestinal Tumor Study Group 1985). Although rates of distant metastases were slightly lower in the two arms that contained chemotherapy, no single arm had a significant impact on distant failure; thus, the survival advantage achieved with combined RCT appeared to relate primarily to the marked reduction in local relapse rates. These result were later confirmed by a trial conducted by the Norwegian Adjuvant Rectal Cancer Project Group (Tveit et al. 1997). Again, the local relapse rate was significantly decreased from 30 to 12% by combined postoperative RCT compared with surgery alone, an effect which also translated into an improvement in 5-year survival, though no significant impact on distant metastases was achieved. The more recent NSABP R-02 also showed that combined RCT resulted in a significantly reduced local failure rate compared with chemotherapy alone (8 vs 13%); however, this small absolute reduction did no longer translate into a difference in overall survival (Wolmark et al. 2000). Evidently, in all these trials, the effect of concomitant 5-FU chemotherapy was primarily mediated through its radiosensitization properties rather than through its own systemic efficacy. This conclusion is further strengthened by a recent Italian study that showed no significant effect on local control and survival when postoperative radiotherapy (RT) and chemotherapy was applied sequentially rather than concomitantly (Cafiero et al. 2003).

The NCCTG 794751 trial was the first to integrate a course of full-dose chemotherapy before as well as

Table 18.1. Randomized trials of postoperative radiation (*RT*), chemotherapy (*CT*), or combined radiochemotherapy (*RCT*) for locally advanced rectal cancer (UICC II and III)

Reference	Treatment	Local failure (%)	Distant failure (%)	Five-year survival (%)
GITSG 7175 (Gastointestinal Tumor Study Group 1985)	Surgery	24	34	45
	Surgery + RT	20 (p=0.08)	30	52 (p<0.05)
	Surgery + 5-FU/MeCCNU	27	27	56
	Surgery + RT+5-FU/ MeCCNU	11	26	59
NCCTG/Mayo 794751 (Krook et al. 1991)	Surgery + RT	25 (p=0.04)	46 (p=0.01)	48 (p=0.025)
	Surgery + RT+5-FU/MeCCNU	13.5	29	58
Norway trial (Tveit et al. 1997)	Surgery	30 (p=0.01)	39	50 (p=0.05)
	Surgery + RT+5-FU	12	33	64
NSABP R-02 (Wolmark et al. 2000)	Surgery + CT[a]	13 (p=0.02)	29	64
	Surgery + RCT	8	31	64
Italy trial (Cafiero et al. 2003)	Surgery + RT	20	38	59
	Surgery + 5-FU/LEV + RT + 5-FU/LEV (RT and CT applied sequentially)	22	27	43

[a]Male patients received MOF (MeCCNU, Vincristin, 5-FU) or 5-FU/leucovorin; female patients only 5-FU/leucovorin