Radiosensitizing agents for the management of rectal cancer

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Introduction

The standard of care of patients with stages II and III adenocarcinoma of the rectum located within 12 cm from the anal verge is preoperative chemoradiation [1,2]. This approach facilitates surgical intervention, which might allow the performance of a low anterior resection versus an abdominoperineal resection (APR). The rate of recurrence has also been shown to be significantly decreased in patients treated with preoperative chemoradiation compared with resection alone (a total mesorectal excision) [3]. Furthermore, data continue to accumulate suggesting that survival advantage in patients subjected to neoadjuvant treatment may also be superior [2,3]. However, the major challenge that we currently face with chemoradiotherapeutic intervention for the management of rectal cancer is the broad and unpredictable response in patients subjected to this modality. In our experience, the vast majority of patients (54%) achieve only a partial response. Twenty-one percent of patients did not respond to this modality and in some cases the tumor continued to grow. However, in the same cohort of patients, we observed a 25% of patients achieving a pathologically complete response (pCR; Fig. 1) [4].

Three major aspects of these observations remain at large: (i) the factors/mechanisms that lead to these differences in a response to ionizing radiation (IR); (ii) identification of patients who are unlikely to respond to chemoradiation; and (iii) the development of novel radiosensitizing modalities to treat patients who do not respond to conventional chemoradiotherapeutic interventions.

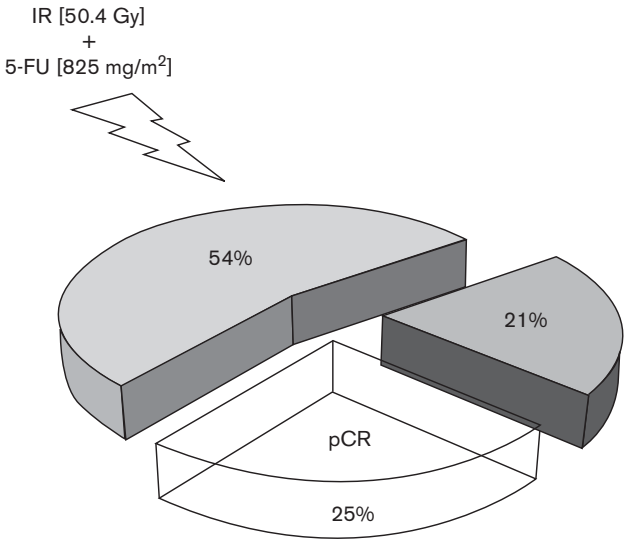
Mechanisms that lead to a difference in a response

There has been a great deal of interest in elucidating pathways that lead to a resistance to IR in rectal cancer [5]. Many pathways are responsible for cell survival/death when injury due to IR is induced (Fig. 2). Apoptosis is, perhaps, the best characterized [6,7], and survivin has been extensively studied as well [8–10]. Survivin inhibition has shown substantial radiosensitization *in vitro* and *in vivo* [10]. Survivin inhibition improves IR-induced cell death by mechanisms beyond caspase-mediated apoptosis. Alternative pathways of cell death may include, (i) mitotic arrest, (ii) cell cycle redistribution, and (iii) impairment in double-strand breaks DNA repair [10]. Survivin mRNA levels were 4.2-fold higher in tumor tissue compared with normal mucosa. High-surviving mRNA levels significantly correlated with an increased risk of tumor relapse [10]. The results from these studies show the possibility of molecular characterization of tumors. Further study with other molecular factors will facilitate our understanding of pathways leading to resistance. In addition, we must think beyond the basal levels of molecules and begin to explore induction and epigenetic changes leading to molecular events that alter the survival of cells exposed to IR.

Molecular predictors of a response to ionizing radiation

A great deal of impetus has occurred over the past few decades in providing individualized treatment based on the molecular characteristics of a tumor. An understanding of the molecular features of tumor progression and how these features predict responsiveness to chemoradiation

Fig. 1



There is a broad response to preoperative ionizing radiation (IR). A total of 117 patients received the same form of neoadjuvant chemoradiation [4]. There was a 25% of pathologically complete response (pCR), a 54% partial response, and 21% of patients did not respond. 5-FU, 5-fluorouracil.

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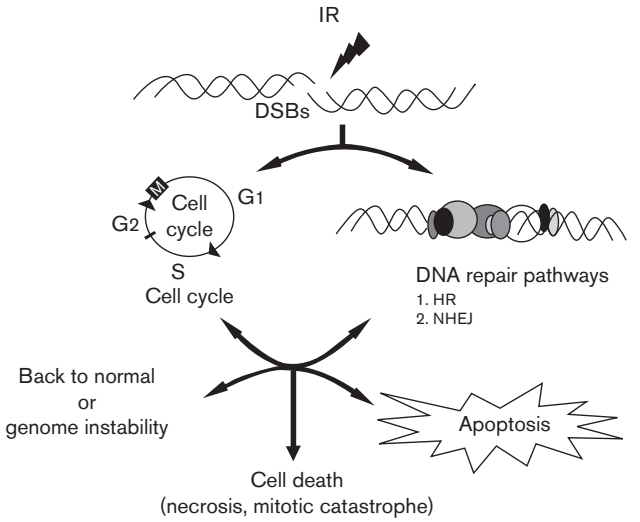
Fig. 2



Ionizing radiation (IR) causes DNA strand breaks. DNA damage sensors are activated. Two major pathways are implicated in the repair of these errors. Homologous recombination (HR) is activated once the cell goes through the S phase of the cell cycle, whereas the nonhomologous recombination end joining (NHEJ) pathway operates in the G1 phase, and it is more error prone. A simultaneous response in DNA damage checkpoints, DNA repair, and a transcriptional response are activated. If the cells are not able to repair the damage induced by IR, apoptosis is activated. Cell death may also occur by other mechanisms such as mitotic catastrophe. DSBs, double-strand breaks.

is growing in an increasingly sophisticated manner. The use of *KRAS* mutation analysis to tailor treatments with or without anti-EGFR therapy is one such widely used example. Survivin may play a similar role in rectal cancer as recently reported by Sprenger *et al.* [11,12]. In this issue of the journal, Dr Kapur summarizes some of the possible pathways that might allow us to tailor treatment in terms of a specific tumor phenotype.

Trimodality treatment for rectal cancer

The current guidelines for the management for stages II and III adenocarcinoma of the rectum mandate a trimodality approach (surgery, chemotherapy, and radiotherapy). Historically, the treatment for low rectal cancer (within 2 cm from the anal verge) involved an APR, which has been a drastic decline over the past 20 years. This technique involves the removal of the distal rectum and perineum with clear tumor radial margins laterally to the pelvic sidewalls. In addition to a permanent ostomy, this procedure is associated with a high rate of perineal wound infections [2]. APR leads to reduced quality of life resulting from a permanent ostomy and worse local control and decreases cancer-specific survival [2]. Whenever possible, low anterior resection should be performed. A total mesorectal excision is the standard of care for patients with rectal cancer [2].

An operation should be planned within 6–10 weeks after the last dose of chemoradiation. A longer window between neoadjuvant chemoradiation and operative intervention (>8 weeks) has been associated with higher rates of pCR (31% >8 weeks vs. 16% <8 weeks) and a decreased rate of 3-year locoregional recurrence (1% for >8 weeks vs. 11% >8 weeks) [13,14].

In Europe, small fractions of IR ($5.0\,\text{Gy} \times 5.0$), for a total of 25.0 Gy, are used. In the United States, the typical IR dose is 45.0–50.4 Gy. In this issue of the journal, Dr Mohiuddin not only discusses dose escalation of these doses, but also timing intervals between treatment modalities in his manuscript addressing new directions in neoadjuvant therapy for rectal cancer.

Radiosensitizing agents in the management of rectal cancer

The observation that some patients subjected to chemoradiation achieve a pCR is a fascinating oncologic outcome as it has been recently shown that this cohort of patients has superior long-term outcomes compared with those who do not achieve a pCR [15]. In this issue of the journal, Dr Habr-Gama *et al.* provide insights in their experience in this cohort of patients and possible avenues to increase the percent of good responders. Historically, 5-fluorouracil (5-FU) has remained the backbone of multiple radiosensitizing modalities in rectal cancer. Dr Patel explores the mechanisms of the radiosensitizing effects of 5-FU and the evolution into its oral form. The substantial progress in the management of colon cancer by the introduction of new chemotherapeutic modalities has led to the rapid inclusion of several of these compounds in the neoadjuvant setting in the management of rectal cancer. A classic example of this scenario stems from the superiority observed with the inclusion of oxaliplatin with 5-FU in the FOLFOX regimen for the management of colon cancer. Although there was limited in-vitro and in-vivo evidence of the efficacy of oxaliplatin as a radiosensitizer, it was rapidly put to use in clinical trials for the management of rectal cancer. A similar history occurred for irinotecan as discussed by Dr Illum. Unfortunately, none of these strategies have shown substantial superiority compared with 5-FU alone, and we have to keep in mind the side effect profile and the cost associated with the introduction of each additional modality. Dr Glynne-Jones provides an excellent review of status of targeted therapies in addition to standard chemotherapeutic agents as radiosensitizers.

As discussed by Dr Mohiuddin, we must expand our horizons to increase the percent of patients with a pCR. Dr Conrad interrogates possible new avenues with the introduction of antiproteosomal agents in the management of rectal cancer. Similarly, our group has investigated novel agents *in vitro* and *in vivo* in an attempt to both elucidate new pathways and provide new radiosensitizing strategies [16,17]. On the basis of the results

of our preclinical observations, our group will begin a phase I trial investigating the effects of new agents in combination with the current standard therapies in the management of rectal cancer. As discussed by all the contributing authors of this issue of the journal, we must continue looking ahead for new strategies. The following manuscripts in this issue of the journal set a strong staging platform.

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