

CHEMORADIATION IN CANCER THERAPY

CANCER DRUG DISCOVERY AND DEVELOPMENT

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Edited by

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*To my wife Sunny and my children Natalie, Alex, and Megan,
whose love and support make my work possible.*

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PREFACE

As the treatment of cancer continues to evolve, clinicians are constantly seeking new and innovative strategies to expand the use of currently available treatment modalities. Among the different strategies to improve therapy, the combining of chemotherapeutic drugs with radiation has perhaps had the strongest impact on current solid tumor treatment practice. This combination has been in use for many decades, but now has become a common treatment option in many clinical settings. This is particularly true for concurrent chemoradiotherapy, which in many recent clinical trials has been shown to be superior to radiotherapy alone in controlling local–regional disease and in improving patient survival. Combining chemotherapeutic drugs with radiotherapy has a strong biologic rationale. Such agents reduce the number of cells in tumors undergoing radiotherapy by their independent cytotoxic action and by rendering tumor cells more susceptible to killing by ionizing radiation. An additional benefit of combined treatment is that chemotherapeutic drugs, by virtue of their systemic activity, may also act on metastatic disease. Most drugs have been chosen for combination with radiotherapy based on their known clinical activity in particular disease sites. Alternatively, agents that are effective in overcoming resistance mechanisms associated with radiotherapy could be chosen. There have been recent clinical successes of concurrent chemoradiotherapy using traditional drugs, such as cisplatin and 5-FU, but these studies have led to extensive research on exploring newer chemotherapeutic agents for their interactions with radiation. A number of new potent chemotherapeutic agents, including taxanes, nucleoside analogs, and topoisomerase inhibitors, have entered clinical trial or practice. Preclinical testing has shown that they are potent enhancers of radiation response and thus might further improve the therapeutic outcome of chemoradiotherapy. Also, there are rapidly emerging molecular targeting strategies aimed at improving the efficacy of chemoradiotherapy. All these important aspects of combined modality therapy in solid tumors are discussed in this book, particularly for tumors that historically have had a poor prognosis and few treatment options.

Curry and Curran review the literature on the combined modality treatment of patients with malignant glioma, focusing on the data from prospective randomized trials, and discuss future directions in research to improve outcome for patients affected by this disease. It is clear that any one systemic agent or multiagent regimen will not have substantial effects on altering the natural history of malignant glioma. A significant improvement in survival will be realized only when improvements in local–regional control are combined with progress in the systemic management of the disease. Specific opportunities to improve surgical and radiotherapy approaches to this disease need to be explored concurrently with development of novel agents targeted to modify the biologic response of these tumors to chemotherapy and radiation. However, novel approaches when combining standard cytotoxic chemotherapy agents with new cytotoxic and cytostatic agents and improved radiotherapy techniques are promising in promoting

decreased radioresistance, toxicities, and possibly increased overall survival of head and neck cancer. Outside of an academic setting, cisplatin and 5-FU still remain the standard of treatment. Though more aggressive, as mentioned in Drs. Eng and Vokes' chapter, these drugs have overall demonstrated improved response rates in locally advanced and recurrent disease. Newer agents will continue to be discovered and provide a basis for further consideration in the treatment of head and neck cancer.

It is apparent that significant progress has been made in improving the outcome of treatment for stage III nonsmall-cell lung cancer, even though there is still a long way to go before victory can be declared. It is clear that radiation alone and surgery alone are inadequate for most stage III disease. Preoperative radiation therapy alone is of limited benefit. Postoperative radiation is controversial, but there may be a limited role in resected N2 patients. For selected stage III cases (N2), there may be a role for surgery after chemoradiation, but this conclusion awaits the outcome of a major phase III study. For inoperable stage III disease, combined modality now appears to be the new standard of care. Concurrent chemoradiation seems to be superior to sequential chemoradiation, but combined sequential followed by concurrent chemoradiation remains under investigation as does consolidative chemotherapy after concurrent chemoradiation. The best results combining chemotherapy with radiation therapy were also seen in limited-stage small-cell lung cancer. At this time, standard treatment for patients with limited-stage small-cell lung cancer is early concurrent twice-daily radiation therapy of 1.8 Gy fractions for a total dose of 45 Gy and platinum-based chemotherapy.

As discussed by Brahmer et al., newer chemotherapy regimens emerge for the treatment of small-cell lung cancer, and these regimens are currently undergoing evaluation for combining chemo- and radiation therapy. As far as esophageal cancer goes, results from surgery alone or primary chemoradiation are equivalent, and both can be offered as options for patients with locally advanced esophageal cancer. The optimal treatment may be based on individual patient selection criteria such as the ability to undergo major surgery, histology, and the location of the tumor. The fact that local recurrence is high despite primary chemoradiation, provides a rationale for tri-modality therapy that includes surgery following preoperative chemoradiation.

The major advance in the treatment of local–regional gastric carcinoma had been the new standard of adjuvant chemoradiotherapy following a curative resection. Laparoscopy is more or less established as a staging procedure prior to surgery. Staging with endoscopic ultrasonography has improved. New strategies will include the use of preoperative approaches and incorporation of new agents. Similar to the carcinoma of the esophagus, the use of molecular markers to predict response and survival is needed. Investigative efforts are underway to further improve the results of multimodality therapy of colorectal carcinoma. In addition to phase III trials discussed in Chapter 14, other studies are incorporating novel chemotherapeutic agents to improve systemic control and radiosensitization, to optimize physical delivery of radiation, and to perform risk stratification with current molecular and genetic techniques. Chronomodulation may have a role in combined modality therapy for colorectal cancer by affecting higher response rates and less stomatitis and neuropathy in metastatic colorectal carcinoma and may become a viable option for treatment of primary disease.

The inferior results with radiotherapy alone compared to cystectomy in patients with muscle-invasive disease have prompted a large number of trials adding systemic chemotherapy to radiotherapy in an attempt to increase local control and eliminate micrometastatic disease frequently present at the time of diagnosis of muscle-invasive disease.

As discussed by Dr. Roth, it is not easy to directly compare surgical series with trials of bladder-sparing approaches. A number of confounding factors can potentially complicate the interpretation of trials of chemoradiotherapy, including the effect of the TURBT on the natural history of this disease, the errors of clinical staging both before and after chemotherapy/radiotherapy, and the endpoints utilized to determine efficacy. Nonetheless, his approach can certainly be offered to patients who are not surgical candidates because of medical co-morbidities, or the occasional patient who refuses surgical intervention. Recent studies in a variety of gynecologic malignancies have convincingly demonstrated that concurrent chemotherapy can significantly improve the outcome of some patients who require radiation therapy for treatment of their disease. Despite the fact that controversies persist about the indications for chemoradiation and ideal drug regimens, the fundamental value in patients with loco-regionally advanced cervical cancer has been established.

The chapter by Dr. Eifel reviews trials of chemoradiation in cervical cancer, including the recent trials that established the value of this approach, and discusses several questions that remain to be resolved regarding this treatment, including the ideal dose and schedule and the effect of chemoradiation on compliance and complications.

One of the most exciting areas of combined modality therapy is the specific molecular targeted therapy in combination with radiation. Over the past decade there has been a quantum increase in the understanding of molecular mechanisms that underlie the process of tumor development, proliferation, invasion, and metastasis.

This has led to a growing awareness of mechanisms by which tumors and normal tissue are able to overcome damage from radiation injury. This knowledge has resulted in a vast amount of preclinical study of ways that these molecular abnormalities may be specifically targeted to result in clinical benefit, not only by potentially impacting on systemic disease, but by enhancing radiosensitivity. The last part of this book describes some of these agents and pathways.

Although we have made significant progress in our understanding of the role of combined modality therapy, much remains to be accomplished. Current and future research may provide exciting opportunities to improve response and survival for patients with tumors previously associated with a dismal prognosis.

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Hak Choy, MD

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