17 Integration of Radiation Therapy and Systemic Therapy for Breast Cancer

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17.1 Introduction

The past decade has arguably been the most exciting time in breast cancer history, as progressive advances in treatment have reshaped the prognosis of patients with this disease. These advances have occurred in all of the disciplines involved in breast cancer treatment, including surgery, radiation therapy, chemotherapy, hormonal therapy, and most recently in biological therapy. The relevance of these advances are very significant on a national scale, as invasive breast cancer remains the most commonly diagnosed cancer in women in the United States, with an estimated incidence of 211,240 cases in 2005 (American Cancer Society 2005). Furthermore, the incidence of breast cancer in the United States is predicted to significantly increase due to the aging population and the increasing percentage of women with delayed childbirth and other risk factors.

The good news concerning breast cancer is that treatment advances are improving outcome. According to the American Cancer Society, the mortality rate for breast cancer patients decreased steadily by 2.3% per year from 1990 to 2001 (American Cancer Society 2005). For patients younger than 50 years of age, the improvement in survival was even more marked, with the mortality rate decreasing by 3.3% per year during the same time period. While some of this improvement has occurred because of increased screening and early detection, improvements in chemotherapy, hormonal therapy, and radiation have also significantly contributed. It is interesting to note that the advances in breast cancer treatment have consisted of a series of incremental improvements. For example, initial studies of systemic treatments indicated that chemotherapy and/or hormonal therapy improved outcome compared with no systemic treatments (Early Breast Cancer Trialists' Collaborative Group 2005). It was then discovered that anthracycline containing regimens offered an advantage over non-anthracycline containing regimens (Early Breast Cancer Trialists' Collaborative Group 2005). Subsequently, more recent studies have shown that the addition of taxanes and the dose scheduling of chemotherapy can also improve out-

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come (Henderson et al. 2003; Mamounas et al. 2005; Martin et al. 2003; Citron et al. 2003). With respect to hormonal therapy, aromatase inhibitors have been found to further improve the benefits of tamoxifen (Early Breast Cancer Trialists' Collaborative Group 2005; Atac Trialists' Group 2005; Thurlimann et al. 2005; Jakesz et al. 2005; Coombes et al. 2004). Finally, modern techniques of delivering radiation have been found to offer an additional improvement in survival of selected patients beyond those achievable with systemic treatment alone (Early Breast Cancer Trialists' Collaborative Group 2000; Van de Steene 2004).

17.1.1 Integration of Chemotherapy/Hormonal Therapy/Biological Therapy with Surgery and Radiation in the Management of Breast Cancer

The majority of breast cancer patients are currently treated with a combination of surgery, radiation, and systemic therapy. This is because all these approaches have proven to be valuable for patients with non-invasive disease, patients with early stage disease, and patients with locally-advanced breast cancer. How to best integrate surgery, radiation, and systemic treatments has become a highly relevant clinical question, and one that affects hundred of thousands of patients each year; therefore, it has become very important for breast cancer patients to be managed by a multidisciplinary team, with participation of the surgeons, radiation oncologists, medical oncologists, pathologists, and diagnostic radiologists. Multidisciplinary management allows for better coordination of each treatment modality, which may increase the efficacy of the combined treatment, while minimizing its toxicity.

This chapter focuses on discussing the role of radiation therapy and systemic therapy in the management of breast cancer, with special emphasis on what is currently known about the optimal integration and sequencing of these treatment modalities.

17.1.2 Non-invasive Breast Cancer: Ductal Carcinoma in Situ

Most patients diagnosed with DCIS are candidates for breast conservation therapy (BCT) and will undergo a lumpectomy as their initial therapy. Data from three randomized trials have indicated that the addition of radiation treatment to the breast after lumpectomy reduces the probability of recurrence. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial, which randomized 818 patients with DCIS to either radiation therapy or observation after lumpectomy, found that radiation therapy decreased the risk of local recurrence at 12 years from 31.7 to 15.7% ($p<0.000005$; Fisher et al. 2001). The European Organization for Research and Treatment of Cancer (EORTC) 10853 trial randomized 1010 patients with DCIS treated with lumpectomy to either radiation therapy or no radiation therapy (Julien et al. 2000). The results of this study also showed that radiation therapy decreased local recurrence (4-year rates 16 vs 9%; $p=0.005$). Finally, a phase-III trial conducted by the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) DCIS Working Party found a similar proportional reduction in breast recurrences with the addition of radiation [UK Coordinating Committee on Cancer Research (UKCCCR) DCIS Working Party 2003].

In addition to radiation therapy, adjuvant tamoxifen has been found to reduce breast recurrence risk. The NSABP B-24 trial randomized 1804 patients with DCIS to either tamoxifen (20 mg daily for 5 years) or no tamoxifen after lumpectomy and radiation therapy (Fisher et al. 2001). The use of tamoxifen led to a significant reduction in the 7-year rates of all breast cancer events, including ipsilateral and contralateral breast recurrences. The NSABP B-35 trial is currently comparing anastrozole, an aromatase inhibitor, against tamoxifen as adjuvant treatment after lumpectomy and radiation therapy for patients with DCIS.

The sequencing of hormonal therapy and radiation for patients with DCIS has never been formally studied. In the NSABP B-24 trial, tamoxifen and radiation therapy were given concurrently without any apparent increase in skin or pulmonary toxicity (Fisher et al. 1999); however, this study did not directly compare concurrent versus sequential use of radiation and tamoxifen for patients with DCIS. This question of sequencing of hormonal therapy and radiation is also relevant to patients with invasive disease and is discussed in greater depth later in this chapter.