Despite nearly two decades of intense investigation, the role of chemotherapy as an adjunct to definitive local treatment (either surgery and/or radiation) of locoregionally advanced squamous cell carcinoma of the head and neck is still being defined. Three ways of integrating chemotherapy into the primary management of this disease have been evaluated: 1) neoadjuvant or induction therapy (chemotherapy preceding local treatment), 2) adjuvant therapy (chemotherapy following local treatment), and 3) concomitant therapy (chemotherapy and local treatment [radiation] given simultaneously). As reviewed previously (1,2), the medical literature is replete with randomized clinical trials that have attempted to demonstrate the value of these different approaches with regard to two major goals: 1) improving survival through enhanced locoregional and systemic control and 2) preserving normal organ function.

Although much of the extant literature is marred by flaws in design or execution that limit an interpretation of the data, a few consistent observations have been gleaned from the best-run studies. In general, neoadjuvant and adjuvant approaches have been associated with modest decreases in the incidence of distant metastases, and neoadjuvant therapy followed by radiotherapy now has an established role in organ preservation of the larynx and hypopharynx (3-9). Thus far, however, a survival benefit for adjunctive chemotherapy has been consistently observed only in studies of concomitant chemotherapy and radiotherapy. With the exception of a recent trial of both concomitant and adjuvant chemotherapy (compared with radiotherapy alone) in the treatment of advanced nasopharyngeal carcinoma, which demonstrated a striking survival advantage for patients in the experimental arm (10), the degree of improvement in survival has been modest. Nevertheless, this trend has been noted in recent reviews (1,2) and its statistcal validity confirmed in a recent meta-analysis (11).

In this issue of the Journal, Merlano et al. (12) report a survival update from perhaps the best-known study utilizing combination, as opposed to single-agent, chemotherapy in a concomitant approach versus radiotherapy alone (13). Originally reported in 1992 with a median follow-up of 35 months, the results of the study were remarkable for a near doubling of the complete response frequency and improved progression-free and overall survival among patients in the experimental arm. Most likely resulting from the alternation of chemotherapy and radiotherapy and the use of bolus (as opposed to infusional) fluorouracil, this advantage was obtained without enhanced severe mucositis, a problem that has plagued other attempts at concomitant treatment, especially when multiple drugs are used.

With a minimum follow-up of 4 years for the treated population, Merlano et al. (12) now confirm the survival benefit accruing to the patients treated with alternating chemotherapy and radiotherapy. This better survival appears to be related to enhanced locoregional control, a recurrent theme in trials that report a benefit for concomitant treatment.

Although this information is quite valuable and Merlano et al. are to be congratulated for making the effort involved in long-term follow-up, interpretation of their findings remains somewhat problematic. First, the trial was prematurely closed to patient accrual because of clinician refusal to enroll additional patients in the radiotherapy-only group once an interim analysis demonstrated an improved complete-response frequency for individuals in the experimental arm. Because no early-stopping rules were incorporated into the protocol at its inception, the risk of bias influencing the results of interim analyses must be factored into an interpretation of the reported P values. Second, the control group seems to have fared worse than might be expected for a similar group treated with definitive radiotherapy. It is tempting to theorize that the control group experience is related to treatment interruptions (>1 week for 25% of the patients) and the relatively low total dose of radiation (mean, 65.6 Gy). These concerns were raised by other investigators when the original report (13) was published, and they continue to cloud the significance of the findings today (14).

The disappointing survival in the combined-treatment arm (24% at 5 years) also bears comment. Although a precise delineation of the causes of death in this arm is not possible from the data reported, it can be inferred that 95% of the deaths occurred among patients with recurrent disease and/or second primary cancers, the latter afflicting 12.5% of the original population and, presumably, a much larger proportion of the population. 

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patients who survived for more than 2 years. As therapy for patients with unresectable disease continues to evolve and improve, efforts to reduce the incidence of second primary cancers will be paramount to the achievement of improved long-term survival (15).

In summary, the data reported by Merlano et al. in this issue of the Journal are provocative, but we are in full agreement with the authors that their approach cannot yet be recommended as standard therapy. Nevertheless, a growing body of evidence indicates that chemotherapy for this patient population is most effective when given in concurrent schedules with radiotherapy (12,11). The efficacy of the combined approach seems directly related to improved control of locoregional disease, which remains the major cause of death among patients with unresectable disease. The path that needs to be followed in the next decade seems to be clear. First, further refinement of concomitant approaches with novel regimens and schedules to enhance antitumor activity while minimizing excessive toxicity must be pursued. Once a significant degree of durable local control is achieved, the integration of additional chemotherapy will be necessary to address the problem of micrometastases. Finally, because long-term survivors of this disease are frequently “victims of success” and fall prey to second cancers, they represent excellent candidates for trials investigating chemopreventive approaches.

References


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