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Evolution of clinical trials in head and neck cancer

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Abstract

The treatment paradigm for locally advanced head and neck cancers has evolved over the past two decades as the role of chemotherapy has been substantiated by clinical trials. Presently, concurrent chemoradiation is considered a standard treatment option for patients with resectable

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head and neck tumors desiring an organ preservation approach, as well as for patients with locally advanced nasopharyngeal cancers and patients in the postoperative setting who are at high risk for recurrence. The addition of a taxane to induction chemotherapy appears to improve efficacy over cisplatin and 5-FU. Targeted biologic therapies such as the monoclonal antibody Cetuximab has demonstrated efficacy with radiation that appear comparable to chemoradiation combinations and has a favorable toxicity profile. This review will discuss key clinical trials supporting the current standard of care. Emerging new technologies such as intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) will also be reviewed. Functional assessments and quality of life issues will be addressed.

Keywords: Head and neck cancer; Clinical trials; Larynx cancer; Oropharynx cancer; Nasopharynx cancer; Induction chemotherapy; Chemoradiation; Intensity modulated radiation therapy (IMRT); Quality of life

1. Introduction

Each year, approximately 45,000 men and women in the United States are diagnosed with a head and neck malignancy [1]. Of these patients, about 60% present with locally advanced disease. Historically, definitive treatment involved radical surgical resection and adjuvant radiation, resulting in approximately 30–70% cure rates [2]. In addition, for the subset of inoperable patients, radiation alone yielded long-term disease free survival of 0–20% [3].

In an attempt to improve cure rates as well as to enhance functional outcome, chemotherapy was investigated as a component of multimodality therapy. The most commonly investigated strategies included the use of induction chemotherapy and the use of concurrent chemoradiation. This review will highlight key clinical trials that have defined the current standard of care for patients with locally advanced squamous cell carcinoma of the head and neck.

2. Induction chemotherapy

There are several mechanisms by which induction chemotherapy may be hypothesized to enhance treatment outcomes in patients with locally advanced head and neck cancer. First, chemotherapy may decrease tumor volume thus decreasing the fraction of hypoxic cells. Hypoxia is a major factor contributing to radiation resistance. In addition, chemotherapy and radiation may act as non-cross resistant modalities, each contributing to tumor cell death. Furthermore, chemotherapy may enhance disease outcome by eliminating clinically occult micrometastatic disease.

The administration of chemotherapy prior to radiation has several hypothetical advantages over its use either concurrently or adjuvantly. Induction chemotherapy may reduce the expression of distant metastasis, particularly in patients at high risk such as those presenting with advanced nodal disease. Second, the toxicities with induction chemotherapy are primarily related to myelosuppression and may allow for less radiation-related mucosal toxicities when not given concurrently. Finally, utilization of concurrent chemotherapy is associated with a significant increase in acute and late effects.

The initial enthusiasm for induction chemotherapy did not come until the 1980s when Kish reported the high response rates to chemotherapy in previously untreated patients with locally advanced head and neck cancer [4]. In this trial, investigators treated inoperable patients with cisplatin and 5-fluorouracil (5-FU) and achieved an overall response rate of 89%. Five of the 26 patients showed a complete remission to this initial therapy. Twelve of the 26 patients ultimately underwent resection of their disease. These results demonstrated the tolerability and potential benefits of induction chemotherapy.

Unfortunately, subsequent trials did not result in a significant difference in overall survival with induction 5-FU/cisplatin chemotherapy. These trials, however, did demonstrate the prognostic value of initial response to chemotherapy in predicting subsequent response to radiotherapy [5–7]. Subsequent clinical trials to further investigate induction chemotherapy (Table 1) can be divided into induction therapy as part of organ preservation and induction therapy for patients with unresectable disease.

2.1. Induction therapy as part of organ preservation

In patients with resectable disease, induction chemotherapy followed by a radiation-based organ preservation approach was investigated. This was most commonly conducted in patients with laryngeal, hypopharyngeal, and base of tongue tumors where surgical resection could lead to significant morbidity. Chemotherapy was utilized as a predictor of radiotherapy responsiveness. Two sentinel randomized phase III trials compared induction chemotherapy followed by radiation to primary surgery and adjuvant radiation. These studies were conducted by the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group [8] and the EORTC [9].

In the VA trial, 332 patients with stages III–IV laryngeal cancer were randomized to either standard of care (total laryngectomy with adjuvant radiation) or induction chemotherapy consisting of 3 cycles of 5-FU and cisplatin with subsequent definitive radiation to 66–76 gray (Gy). Tumor response to induction chemotherapy was assessed after the second cycle, with patients with response undergoing the third cycle. Those without response or who had recurrence following chemotherapy and radiation were subject to salvage laryngectomy [8].

Complete response after two cycles of chemotherapy was observed in 31% of patients, and partial response seen in 54%. Local recurrence was significantly ($p = 0.0005$) increased in the induction chemotherapy/radiation arm, but fewer dis-