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Salvage of recurrence after surgery and adjuvant therapy: A systematic review☆,☆☆

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ABSTRACT

Purpose: To determine the oncologic and functional outcomes of patients undergoing salvage surgery for recurrent head and neck squamous cell carcinoma after initial management with surgery and adjuvant therapy.
Data sources: Ovid Medline, Embase, Scopus, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and Clinicaltrials.gov.
Review methods: A structured search was performed of the literature to identify studies that included patients undergoing surgical salvage for local, regional, or locoregional recurrent head and neck squamous cell carcinoma without known distant metastases who had been treated with initial surgery and post-operative adjuvant radio- or chemoradiotherapy. Studies were excluded if they did not report at least 1-year survival estimates, included patients who underwent primary non-surgical management, or included those treated with non-surgical salvage therapies or supportive care alone.
Results: The search strategy yielded 3746 abstracts. After applying exclusion and inclusion criteria, 126 full-texts were reviewed and six studies were included with a total of 222 patients. All studies were retrospective in design and included diverse disease subsites and stages. Complications and functional outcomes were inconsistently reported. Five-year survival estimates ranged between 10% and 40% between studies.
Conclusions: Patients undergoing salvage surgery for recurrent head and neck squamous cell carcinoma after initial surgery and adjuvant therapy may have a particularly poor prognosis. Future studies are needed to determine functional and quality of life outcomes in this patient population and to identify specific prognostic factors for re-recurrence and survival.

1. Introduction

In 2017, an estimated 49,670 patients in the United States will be diagnosed with cancers of the oral cavity or pharynx and another 9700 patients will die of their disease [1]. Up to 30% of patients who undergo definitive treatment for advanced head and neck cancer may experience a local and/or regional recurrence [2]. In patients with unresectable recurrent or metastatic squamous cell carcinoma of the head and neck, median survival with supportive care and chemotherapy alone is less than one year, even with current combinations of platinum agents and epidermal growth factor receptor inhibitors [3]. Recent trials with immunotherapy show only a modest improvement in overall survival over standard chemotherapy [4]. Reirradiation is an option in select patients and can achieve long-term survival. Oncologic control, however, may be higher for salvage surgery in resectable disease, and reirradiation can lead to severe late toxicity including treatment-related deaths in up to 10% of patients [5].

For these reasons, surgery is the current mainstay of management for recurrent resectable disease although long-term survival after surgical salvage is, generally, less than 40% [6]. Survival outcomes, however, are influenced by multiple patient and treatment factors, the anatomic boundaries of the head and neck, and the intrinsic pathobiology of recurrent disease. Laryngeal recurrences appear to have higher overall salvage rates than oral cavity, oropharyngeal, or hypopharyngeal sites [7,8]. Both advanced initial and recurrent disease staging as well as a short disease-free interval have been associated with

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decreased survival after salvage surgery [6,8–12].

The initial treatment modality, as well, is a critical factor in the resectability of recurrent disease and outcomes of salvage attempts. Much of the current data on management of recurrent head and neck cancer examines outcomes and prognostic factors for salvage surgery after initial definitive non-surgical management [6,7]. Nonetheless, upfront surgery with adjuvant therapy remains an important treatment paradigm in the management of head and neck cancer, particularly for oral cavity sites and, with the increasing use of transoral surgery for HPV-related disease, for oropharyngeal sites as well. Few reports, however, specifically analyze outcomes of patients who have undergone primary surgery followed by adjuvant radio- or chemoradiotherapy and subsequently recurred. This specific patient group, who often experience recurrent disease in previously dissected and radiated tissue planes, may have a worse prognosis than those who underwent primary non-surgical management [11,13–17]. The purpose of this systematic review is to characterize the oncologic and functional outcomes of patients undergoing salvage surgery after prior surgery and adjuvant therapy and to identify prognostic factors for this specific patient subset.

2. Methods

2.1. Search strategy

The published literature was searched using strategies created by a medical librarian for salvage surgery for recurrence after treatment of head and neck cancer. The search strategies were established using a combination of standardized terms and key words, and were implemented in Ovid Medline 1946-, Embase 1947-, Scopus 1960-, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and Clinicaltrials.gov. All searches were completed in May 2017. Results were exported to Endnote for a total of 7364 citations. The automatic duplicate finder in EndNote was used and 3618 duplicates were assumed to be accurately identified for a total of 3746 unique citations.

2.2. Inclusion and exclusion criteria

Studies were included if they evaluated oncologic outcomes of patients who underwent initial surgery with post-operative (chemo) radiotherapy for head and neck squamous cell carcinoma who had local, regional, or locoregional recurrence without known distant metastases and were subsequently treated with surgical salvage with or without adjuvant chemotherapy or re-irradiation. Minimum oncologic outcomes considered for inclusion were 1- or more year survival statistics (overall, disease-specific, or disease-free survival). Studies were excluded if 1) they included patients who had undergone other initial treatment modalities (surgery alone or definitive non-surgical therapy); or 2) included patients undergoing non-surgical salvage therapies or supportive care alone with those undergoing surgical salvage in survival analyses; or 3) included non-head and neck primary subsites or pathologies other than squamous cell carcinoma; or 4) examined second salvage attempts after re-recurrence; or 5) reported on the outcomes of a patient population already described in a separate article. Non-English studies were included when possible with use of online translation software (Google Translate; Google, Mountain View, CA). If they could not be adequately interpreted to extract the appropriate data, these studies were excluded. Two reviewers (J.Z. and P.P.) screened titles and abstracts for inclusion in full-text review and data extraction.

2.3. Data extraction and study outcomes

A data extraction spreadsheet (Microsoft Excel 2016; Microsoft, Redmond, WA) was created and full-texts were independently reviewed by two authors (J.Z. and P.P.). Variables of interest included trial time period, sample size, head and neck primary subsites, HPV-status if known, initial and recurrent tumor staging, initial and salvage treatment modalities, complications, oncologic outcomes (overall, disease-specific, and/or disease-free survival), and prognostic factors associated with survival. When full-texts were excluded, reasons were recorded.

2.4. Quality and risk of bias

To assess study quality and risk of bias, the Methodological Index for Non-Randomized Studies (MINORS) criteria was used [18], as all included studies were retrospective in design. The eight essential components of the MINORS criteria were assessed including 1) a clearly stated aim, 2) inclusion of consecutive patients, 3) prospective data collection, 4) appropriate study endpoints, 5) unbiased assessment of the study endpoint, 6) appropriate follow-up period, 7) loss to follow up less than 5%, 8) prospective calculation of the study size. Study quality and risk of bias were reviewed independently by two authors (J.Z. and P.P.).

2.5. Statistical analysis

The authors undertook this systematic review with the intent of performing a meta-analysis to summarize the results from included studies. Due to heterogeneity in the way outcomes were reported between studies, however, it was not possible to perform a meta-analysis. Thus, a qualitative analysis was performed.

3. Results

3.1. Study selection

The search strategy identified 3746 unique citations and abstracts from these articles were screened for inclusion in full-text review. One hundred twenty-six full texts were analyzed and of these 120 were excluded. Reasons for exclusion are stated in Fig. 1.

3.2. Study characteristics

Six studies met inclusion criteria (Table 1), reporting on a total of 222 patients with a median of 13 patients (range 8 to 104 patients) per study, published between 1986 and 2017. In addition to patients treated with surgery and adjuvant therapy prior to recurrence, five studies examined patients undergoing other initial treatment modalities, including surgery alone and definitive non-surgical management. Patients undergoing surgical salvage after initial treatment with surgery and adjuvant therapy made up 28% to 100% of each study's entire cohort. Demographics and treatment characteristics, including initial and recurrent staging, disease-free interval, and high-risk pathological features were detailed in four studies for all patients undergoing salvage surgery but were not recorded specifically for those patients treated with initial surgery and adjuvant therapy. Two studies included only salvage of recurrent neck disease, one of which involved carotid resection in all cases.

3.3. Quality and heterogeneity

Study quality as assessed by the MINORS criteria is shown in Table 2. Median score was 7.5 (range 7 to 10) out of 16 possible points. Although survival estimates are given for patients who underwent salvage surgery after prior surgery and adjuvant therapy, no study reported confidence intervals around these estimates. Additionally, the absence of baseline patient and tumor characteristics for this group and the heterogeneity of primary tumor subsites limits comparison of survival estimates between studies. No study prospectively gathered data or calculated sample size.