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Survival and selected outcomes of older adults with locally advanced head/neck cancer treated with chemoradiation therapy

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Abstract

Objectives—Chemoradiation therapy (CRT) remains a potentially curative treatment in patients with locally advanced head/neck cancer (LA-HNC). However, survival and other outcomes in older patients with head/neck cancer receiving chemoradiotherapy are not well established. This study was performed to elucidate selected outcomes in this patient population.

Materials and Methods—Retrospective study of LA-HNC patients 70 years of age who had received 5-fluorouracil-hydroxyurea-based CRT with a minimum of 3 years of follow up after therapy initiation was performed. Pre-treatment patient- and cancer-related characteristics were recorded. Survival data in addition to gastrostomy tube utilization, swallowing function, and hematologic toxicity were captured.

Results—Eighty-nine patients treated between 1997 and 2009 were eligible for analysis (median age, 76 years; range, 70–94; male, 61%; ECOG PS, 0–1 43%; stage IVA/B, 71%). 86 were evaluable for survival analysis. 5-year overall and event-free survival were both at 32% with a median follow-up time of 39.2 months. The majority (86.5%) were able to complete all planned treatment cycles. A significant proportion of patients, however, required gastrostomy tube during

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CRT (62%) and developed aspiration during swallowing evaluation post-treatment (44%). Several patients required hospice (9%) or skilled nursing facility (13%) referrals during treatment.

Conclusion—Select older adults with LA-HNC can still experience long-term benefits despite 5-year survival rates lower than those historically reported in younger patients undergoing identical CRT regimens although potentially at higher risk for acute toxicities. Assessment and selection of those who can tolerate more intense combined-modality strategies and their long-term outcomes merit further larger, prospective studies.

Keywords

Elderly; Geriatric; Head/neck cancer; Chemoradiation; Combined modality; Outcomes; Survival; Geriatric; Aspiration; Gastrostomy tube

1. Introduction

Despite the rise of human papillomavirus-related oropharyngeal cancers among relatively younger adults, head and neck cancers remain a common cancer among older adults, with a median age of diagnosis in the early 60s, with over half of affected patients diagnosed with locally advanced disease (i.e., stages III–IVB).¹ As a result, concurrent chemoradiotherapy (CRT) remains a potentially curative treatment approach for the majority of these patients. The use of CRT has led to improved organ preservation, locoregional control rates of up to 95%, and 3 to 5 year progression-free survival (PFS) and overall survival (OS) rates approaching 60–80% and 60–70%, respectively.^{2–8}

However, the role of CRT in older adults with locally advanced head/neck cancer (LA-HNC) remains under-explored for several reasons. There is evidence that CRT confers an absolute survival benefit based on a recent meta-analysis of clinical trial data.^{8,9} However, older adults are under-represented in cancer clinical trials in general¹⁰ and several of the seminal CRT studies either excluded older adults or had patients with a median age 60 years, often incorporating cisplatin-based chemotherapy that might be more difficult to administer safely to older adults.^{2–4,6} Single institution-based studies have demonstrated that older adults with LA-HNC may still derive similar benefits of locoregional control and survival with CRT.^{11–13} These potential benefits, however, are tempered by higher risks for toxicity. Chemotherapy for relapse and metastatic disease in older adults with head/neck cancer can achieve similar response rates and time to progression benefits, yet with higher attendant risks such as increased rates of renal, gastrointestinal and hematologic toxicities.¹⁴ Similar findings have also been demonstrated with radiotherapy including observations that advanced age is a risk factor for late radiotherapy related toxicities such as swallowing dysfunction, fistula formation and gastrostomy tube dependence.^{15–17}

These knowledge gaps in assessing the role of CRT in older adults with LA-HNC have led us to examine our own institutional experience in those aged 70 years and older who have undergone CRT. The aim of this study was to qualitatively examine the following key clinical outcomes in this patient cohort: event-free and overall survival; hematologic and non-hematologic treatment-related toxicities; unplanned hospitalizations and their reasons for admission; and rates of gastrostomy tube placement and retention.

2. Patients and Methods

This is a retrospective medical record review of patients with newly diagnosed, head/neck squamous cell carcinomas (excluding nasopharynx and salivary gland tumors) with stages II–IVB disease treated with definitive concurrent CRT at the University of Chicago Medical Center from January 1, 1997 to October 1, 2009. Patients were identified through our internal head/neck cancer database in radiation oncology, which included patients both on and off study protocols. The date of the last review for this study was September 1, 2012. Institutional review board approval was obtained prior to initiation of the study. Patients with stage II cancers deemed “high-risk” (e.g., unresectable tumor with estimated 2-year life expectancy 10% with RT alone) recommended to receive definitive CRT by the treatment team through tumor board consensus were also included based on the institution’s experience in this group.^{18–20} Limited surgical resection prior to CRT was allowed if it had been part of diagnostic and/or staging purposes. Treatment strategies incorporating induction chemotherapy and/or alternative radiation dosing (hyperfractionated and/or accelerated) were permitted for study inclusion. All patients were required to have been at least 70 years of age at the start of CRT. The majority of patients received 5-fluorouracil-hydroxyurea (FHX)-based CRT regimens during scheduled hospitalizations, whether on- or off-study, as part of the institution’s preference for FHX-based regimens, which allows for avoidance of cisplatin-based toxicity and relatively more intensive radiotherapy strategies. Details of these combination regimens, including dosages and frequencies, have been described in prior studies.^{18,19,21–25}

All patients were deemed generally fit to undergo CRT by a multidisciplinary team. All pre-treatment (i.e., baseline) evaluations included a history and physical examination; baseline laboratory testing including complete blood count and serum chemistries; swallowing evaluation incorporating a videofluoroscopic swallowing (VFS) examination; and CT imaging of the neck and chest. Comorbidity at baseline was captured utilizing the Charlson comorbidity index, excluding cancer diagnosis.²⁶ This score is summated with each comorbid condition assigned a different numerical value, with higher total scores associated with higher one-year mortality. Gastrostomy tube for nutritional support was recommended and placed when severe mucositis and/or dysphagia led to significantly decreased oral intake resulting in signs of severe dehydration, severe protein/calorie malnutrition, and/or weight loss 10% of baseline. Because of insufficient data and lack of routine evaluation in the records, other clinical factors such as tobacco use, alcohol use, human papillomavirus (HPV) status of the tumor, level of social support, and prior radiation exposure were not included a priori for analysis.

Event-free survival, overall survival and cause of death were assessed and recorded for up to 5 years post-CRT completion. Treatment response data were incomplete for many patients, so this was not included in the analysis (data not shown). Cumulative incidence of gastrostomy tubes was examined. In addition, the time from day 1 of CRT to gastrostomy tube placement (days) (i.e., gastrostomy tube placement latency) as well as time of tube placement to time of tube removal (days) (i.e., gastrostomy tube retention) was examined. Rates of gastrostomy tube revision and/or replacement were also recorded. Rates of

aspiration were also evaluated with serial VFS examinations prior to, within one month of completion of, and at 6 and at 12 months following CRT if recorded.

Frequency, severity, and types of hematology/non-hematologic toxicities utilizing the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, were evaluated.²⁷ Unplanned hospitalizations (i.e., hospitalizations during the off-week given the q2 week CRT schedule) during the course of CRT were examined and recorded, including the reason for admission and any salient adverse clinical events that were encountered during review of their hospitalization course. The event-free survival (EFS; defined as time to disease progression or death) and overall survival (OS; time to death regardless of cause) were calculated by utilizing the Kaplan–Meier method performed with SPSS v. 20 software (Armonk, NY). Since this study was of a qualitative nature a priori, descriptive statistics were employed (i.e., frequencies, percentages, mean, median, range) in the analysis of the other outcomes.

3. Results

A total of 89 patients were included. Baseline characteristics included 52 males (58%) with a median age at diagnosis of 75.7 years (range 70–94) and at first treatment of 76.4 years (range 70–94) (Table 1). Primary cancer sites included mostly the oral cavity (37%) and the oropharynx (44%). The majority of patients (71%) had stage IVA–B cancers. Inclusion of those patients with high-risk stage II cancers (12% of the total cohort) did not significantly alter results of the toxicity or survival analyses; thus, they remained in the cohort analyzed (data not shown). Baseline ECOG (Eastern Cooperative Oncology Group) performance status was 0–1 in 43% of patients, 2–3 in 9%, yet unknown (i.e., not documented) in 48% of patients. The median baseline Charlson comorbidity index (excluding cancer as a diagnosis) was 1 (range, 0–5). The majority of chemotherapy regimens were FHX-based (87%), with specific regimens delineated in Table 1. Up to 42% of patients received once-daily radiation and 47% received twice-daily radiation (Table 1). The majority of patients were able to complete all planned CRT cycles (N = 77, 86.5%). Of those able to complete all planned CRTs, chemotherapy dose reductions occurred in at least 14 (18%).

Survival data were available in 86 patients with a median follow-up time of 39.2 months (range, 32.5–143.1 months). Median overall survival was 25.1 months with an estimated 5-year overall survival (OS) of 32%. Median event-free survival (EFS) was 18.2 months, with a 5-year EFS of 32%. Based on exploratory analyses, there was no significant difference in either OS or EFS based on primary site, cancer stage, or type of treatment regimen, including whether patients received induction chemotherapy or radiotherapy fractionation (data not shown). There was a significant decrease in EFS by 1 year: in the 30 deaths recorded by this time-point, approximately 43% were due to treatment-related toxicities or complications; 20% due to disease recurrence or progression; 20% due to unknown causes; 10% due to comorbid conditions; and 7% due to second cancers (full data not shown).

Gastrostomy tube utilization (i.e., time to placement and retention) was assessed (Table 2). A total of 68 patients required gastrostomy tube placement (77%), with the majority being placed during CRT (62%). Of those tubes being placed during CRT, only 8 were placed

within the first week of treatment (19%; data not shown). Due to insufficient long-term data (i.e., approximately 30% of evaluable patients are missing follow-up data), gastrostomy tube dependence could not be evaluated. Of the patients evaluated for rates of aspiration, 70 patients (79%) had baseline swallowing function data available. Although long-term follow-up swallowing study data were sparse, over 40% of evaluable patients developed signs of aspiration on VFS examination within 1 month of CRT completion, with the majority of those at 6-month follow-up having persistent aspiration (Table 2).

As for toxicity, grades 3–4 neutropenia occurred in 30 patients (34%); grade 3 anemia in 10 patients (11%; no grade 4); and grades 3–4 thrombocytopenia in 8 patients (9%). Data on non-hematologic toxicity such as dermatologic toxicity was insufficiently captured. Mucositis was not consistently graded in the record; however, 8 patients did have grade 4 mucositis (9%). No unplanned hospitalizations during the treatment course were encountered, yet several hospitalizations occurred within 4 weeks of CRT completion. Inclusive of this longer observation period, the following adverse clinical events were identified up to 1 month post-CRT: neutropenic fever (N = 13); bacteremia without sepsis (N = 11); sepsis (N = 9); respiratory failure of any cause (N = 7); delirium (N = 9); death in the medical intensive care unit (N = 6); hospice referral (N = 8); and skilled nursing referral for placement (N = 12).

4. Discussion

In the current study, which is one of the largest case series of CRT-based outcomes in patients aged ≥70 years with LA-HNC, we demonstrated that such approaches are feasible; can lead to long-term survival in approximately one-third of patients; and can be achieved with reasonably acceptable grades 3–4 treatment-related hematologic toxicities. We have learned from prior studies that older adults can tolerate more intensive chemotherapy and radiotherapy approaches with similar response and survival outcomes.^{14,28,29} However, few studies exist in evaluating the risks and benefits of CRT in this population. Two studies have shown feasibility with the oral chemotherapy agent S-1 in older adults with LA-HNC in terms of overall response rates (>50% across stages), but survival and long-term functional outcomes remain lacking.^{30,31} One of the earliest retrospective studies evaluated 40 patients with LA-HNC aged ≥70 years undergoing adjuvant CRT with 80% being able to complete all planned CRT treatments.¹¹ More recent studies have evaluated definitive CRT as a feasible, organ-sparing approach in older adults with LA-HNC, combining CRT with induction chemotherapy and/or more intensive radiotherapy regimens.^{12,13} For comparison, these studies' findings are summarized in Table 3.

Despite comparable follow-up and completion rates, the OS rate (32%) in our cohort was relatively lower than that of other studies (Table 3). Although not directly comparable, our event-free survival (EFS) was lower than the disease-free survival (DFS) and PFS demonstrated in these studies, ranging from 58 to 71%, with smaller studies in older LA-HNC CRT patients demonstrating similar DFS and OS rates even after adjusting for comorbidity or HPV-status.³² In terms of survival trends, our OS and EFS remain somewhat lower than those reported by Michal et al., which also included use of twice-daily radiation CRT regimens, when compared to the other 2 studies, which incorporated exclusively once-

daily RT schedules. Nevertheless, these survival rates still remain somewhat lower when compared to those with FHX-based regimens evaluated in prior studies at our institution, with 3-year PFS and OS 63–80% and 60–70%, respectively.³³ A relatively higher prevalence of lower performance status and higher median age of patients might have also disproportionately influenced our observed survival rates. Furthermore, many of the early deaths around 1 year post-CRT were, indeed, related to treatment morbidity and not due to cancer (recurrent or synchronous). We do know that the risk for competing mortality is higher for patients with advanced age and/or comorbidity than for those treated with CRT for LA-HNC.¹³ Interestingly, our study's patients were not significantly different in their patient, treatment, comorbidity, or cancer-related characteristics compared to those who were able to achieve longer survival (data not shown). Whether this represented a more vulnerable or frail subset of older patients with an inherently higher risk for acute toxicities that might have accounted for these differences requires further prospective investigation.

In terms of acute treatment-related toxicities, the percentage of patients able to complete all planned cycles of CRT in our study is similar to that encountered in each of the aforementioned studies (i.e., >80%). Regarding hematologic toxicities, historical rates are summarized utilizing select studies of older adults receiving cisplatin-based CRT and younger adults with FHX-based CRT, with rates of hematologic toxicities in our study being generally lower than those reported in the prior studies of older adults with LA-HNC undergoing cisplatin-based CRT but comparable to those seen in FHX-based studies with relatively younger patients (Table 3). Our rate of grade 4 mucositis was not higher than that previously reported for FHX-based CRT.^{18,19,21–25} Moreover, our data did not fully capture the extent and types of non-hematologic toxicities for further comparison.

Our study's gastrostomy tube rate of placement during CRT (49%) was less than that reported in the study by Michal et al. (89%).¹² However, the latter study did not specify the proportion of tubes placed during the course of CRT. Our findings also contrast with those of the other studies, one of which showed that only 15% of patients received feeding tubes (i.e., nasogastric) prior to CRT but those placed during CRT were not reported in the adjuvant setting, whereas the other did not report any feeding tube-related data.^{34–37} When other studies among patients receiving CRT for head/neck cancers in general are examined, the rates of gastrostomy tube placement during CRT can range from 32 to 39%.³⁸ A recent Medicare claims-based study in older adults treated with CRT found similar rates of placement during treatment at 35%.¹³ Unfortunately, our study could not capture rates of gastrostomy tube dependence in this population to confirm a longer duration of gastrostomy tube dependence previously reported.^{39–41}

Furthermore, aspiration rates in our study were higher than those generally reported in younger patients with LA-HNC undergoing CRT, both at baseline (29%) and at the time of completion of therapy (44%) compared to 0–17% and 23–33% depending on the study design and patient population.^{37,42} We know that worse swallowing function with CRT and/or higher rates of aspiration tend to be seen with advanced age as a predictor in this cancer population.^{43–45} Moreover, older adults can have baseline swallowing impairment due to aging and/or comorbid conditions,^{46–48} thus serving as potential explanations for our observation of a relatively higher prevalence of aspiration pre-treatment and increased

incidence of aspiration on serial swallowing studies seen in our study. Because of the retrospective nature of the study, it is unclear how many of the identified cases of respiratory failure or infectious complications were attributable to aspiration.

Despite the inpatient administration of CRT at our institution and lack of unplanned hospitalizations observed, the adverse clinical events captured including those pertaining to nursing home referrals and documented cases of delirium are noteworthy, suggesting that geriatric syndromes are common in this population. Consequently, some have advocated for the incorporation of a geriatric assessment when evaluating older adults with LA-HNC before and during treatment because of these inter-related issues unique to this patient population.^{49,50} In studies evaluating older adults with cancer undergoing chemotherapy, measures from a geriatric assessment have been predictive of chemotherapy-related toxicity, but patients with head/neck cancers, let alone those undergoing CRT, were under-represented.

Nevertheless, we realize that there are several limitations to the current study. First, the retrospective chart review limited our ability to capture functional outcomes, treatment-related toxicities, and other long-term clinical data in many of our study's patients and limited further analysis evaluating other predictors (e.g., tobacco use, HPV status) of survival and other outcomes. Second, our study allowed for several FHX-based chemotherapy regimens, the use of induction chemotherapy, and different RT frequencies to be included, which might have affected toxicity and survival outcomes disproportionately compared to other studies where there was more homogeneity in treatment regimens. We also realize that many institutions do not employ FHX-based CRT regimens compared to platinum- or cetuximab-based CRT, thus limiting generalizability. Third, our institution is a tertiary referral center, which likely introduced bias in patient selection for CRT; therefore, our findings may not be generalizable to older adults with LA-HNC undergoing CRT in the community. Whether our observed survival rates were influenced by increased use of induction chemotherapy or more intense RT regimens in an older LA-HNC patient population remains unclear. Finally, our inability to capture geriatric outcome data and measures of frailty that are important in a geriatric oncology population also limited our ability to better risk-stratify for treatment tolerability and overall prognosis.

Our study is one of the largest reports of adults 70 years or older undergoing CRT for LA-HNC. It demonstrates the feasibility of CRT in the majority of select older adults with LA-HNC treated at a tertiary care center with excellent completion rates and reasonable hematologic toxicity. However, we did note overall survival, gastrostomy tube utilization, and persistent aspiration tended to be poorer than those generally reported in younger patients undergoing CRT. We also noted that several geriatric-specific adverse events were demonstrated during therapy and the immediate recovery period, which may instigate oncologists to have increased vigilance when evaluating these patients for relatively more intense CRT regimens. Thus, a geriatric assessment may be useful to help risk-stratify those older adults with LA-HNC who may truly benefit from CRT. Ultimately, larger prospective studies will be needed to evaluate survival, toxicities, and functional outcomes in older adults with LA-HNC undergoing CRT. Such data will help guide more tailored interventions

to mitigate these risks as well as improve patient selection for CRT in this vulnerable population.

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REFERENCES

1. Seiwert TY, Cohen EE. State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer*. 2005; 92(8):1341–1348. [Epub 2005/04/23]. [PubMed: 15846296]
2. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003; 349(22):2091–2098. [Epub 2003/12/03]. [PubMed: 14645636]
3. Bernier J, Dornge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004; 350(19):1945–1952. [Epub 2004/05/07]. [PubMed: 15128894]
4. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004; 350(19):1937–1944. [Epub 2004/05/07]. [PubMed: 15128893]
5. Adelstein DJ, Saxton JP, Rybicki LA, Esclamado RM, Wood BG, Strome M, et al. Multiagent concurrent chemoradiotherapy for locoregionally advanced squamous cell head and neck cancer: mature results from a single institution. *J Clin Oncol*. 2006; 24(7):1064–1071. [Epub 2006/03/01]. [PubMed: 16505425]
6. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006; 354(6):567–578. [Epub 2006/02/10]. [PubMed: 16467544]
7. Bhide SA, Ahmed M, Barbachano Y, Newbold K, Harrington KJ, Nutting CM. Sequential induction chemotherapy followed by radical chemo-radiation in the treatment of locoregionally advanced head-and-neck cancer. *Br J Cancer*. 2008; 99(1):57–62. [Epub 2008/06/19]. [PubMed: 18560402]
8. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol*. 2011; 100(1):33–40. [Epub 2011/06/21]. [PubMed: 21684027]
9. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. 2009; 92(1):4–14. [Epub 2009/05/19]. [PubMed: 19446902]
10. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003; 21(7):1383–1389. [Epub 2003/03/29]. [PubMed: 12663731]
11. Airolidi M, Cortesina G, Giordano C, Pedani F, Gabriele AM, Marchionatti S, et al. Postoperative adjuvant chemoradiotherapy in older patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2004; 130(2):161–166. [Epub 2004/02/18]. [PubMed: 14967744]
12. Boscolo-Rizzo P, Muzzi E, Trabalzini F, Gava A, Stellin M, Da Mosto MC. Functional organ preservation after chemoradiotherapy in elderly patients with loco-regionally advanced head and neck squamous cell carcinoma. *Eur Arch Otorhinolaryngol*. 2011; 268(9):1349–1355. [Epub 2011/01/25]. [PubMed: 21258812]
13. Michal SA, Adelstein DJ, Rybicki LA, Rodriguez CP, Saxton JP, Wood BG, et al. Multi-agent concurrent chemoradiotherapy for locally advanced head and neck squamous cell cancer in the elderly. *Head Neck*. 2012; 34:1147–1152. [Epub 2011/10/25]. [PubMed: 22021098]

14. Argiris A, Li Y, Murphy BA, Langer CJ, Forastiere AA. Outcome of elderly patients with recurrent or metastatic head and neck cancer treated with cisplatin-based chemotherapy. *J Clin Oncol.* 2004; 22(2):262–268. [Epub 2004/01/15]. [PubMed: 14722034]
15. Schofield CP, Sykes AJ, Slevin NJ, Rashid NZ. Radiotherapy for head and neck cancer in elderly patients. *Radiother Oncol.* 2003; 69(1):37–42. [Epub 2003/11/05]. [PubMed: 14597355]
16. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol.* 2008; 26(21):3582–3589. [Epub 2008/06/19]. [PubMed: 18559875]
17. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2009; 73(2):410–415. [Epub 2008/07/19]. [PubMed: 18635320]
18. Salama JK, Haraf DJ, Stenson KM, Blair EA, Witt ME, Williams R, et al. A randomized phase II study of 5-fluorouracil, hydroxyurea, and twice-daily radiotherapy compared with bevacizumab plus 5-fluorouracil, hydroxyurea, and twice-daily radiotherapy for intermediate-stage and T4N0–1 head and neck cancers. *Ann Oncol.* 2011; 22(10):2304–2309. [Epub 2011/02/19]. [PubMed: 21330337]
19. Seiwert TY, Haraf DJ, Cohen EE, Stenson K, Witt ME, Dekker A, et al. Phase I study of bevacizumab added to fluorouracil- and hydroxyurea-based concomitant chemoradiotherapy for poor-prognosis head and neck cancer. *J Clin Oncol.* 2008; 26(10):1732–1741. [Epub 2008/04/01]. [PubMed: 18375903]
20. Brockstein B, Haraf DJ, Stenson K, Sulzen L, Witt ME, Weichselbaum RW, et al. A phase I–II study of concomitant chemoradiotherapy with paclitaxel (one-hour infusion), 5-fluorouracil and hydroxyurea with granulocyte colony stimulating factor support for patients with poor prognosis head and neck cancer. *Ann Oncol.* 2000; 11(6):721–728. [Epub 2000/08/15]. [PubMed: 10942062]
21. Haraf DJ, Kies M, Rademaker AW, Stenson K, Mittal B, Pelzer H, et al. Radiation therapy with concomitant hydroxyurea and fluorouracil in stage II and III head and neck cancer. *J Clin Oncol.* 1999; 17(2):638–644. [Epub 1999/03/18]. [PubMed: 10080609]
22. Kies MS, Haraf DJ, Rosen F, Stenson K, List M, Brockstein B, et al. Concomitant infusional paclitaxel and fluorouracil, oral hydroxyurea, and hyperfractionated radiation for locally advanced squamous head and neck cancer. *J Clin Oncol.* 2001; 19(7):1961–1969. [Epub 2001/04/03]. [PubMed: 11283128]
23. Vokes EE, Stenson K, Rosen FR, Kies MS, Rademaker AW, Witt ME, et al. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hydroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. *J Clin Oncol.* 2003; 21(2):320–326. [Epub 2003/01/15]. [PubMed: 12525525]
24. Haraf DJ, Rosen FR, Stenson K, Argiris A, Mittal BB, Witt ME, et al. Induction chemotherapy followed by concomitant TFHX chemoradiotherapy with reduced dose radiation in advanced head and neck cancer. *Clin Cancer Res.* 2003; 9(16 Pt 1):5936–5943. [Epub 2003/12/17]. [PubMed: 14676118]
25. Cohen EE, Haraf DJ, Kunnavakkam R, Stenson KM, Blair EA, Brockstein B, et al. Epidermal growth factor receptor inhibitor gefitinib added to chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol.* 2010; 28(20):3336–3343. [Epub 2010/05/26]. [PubMed: 20498391]
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987; 40(5):373–383. [Epub 1987/01/01]. [PubMed: 3558716]
27. National Cancer Institute; 2012. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. http://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm [Accessed September 1, 2012]
28. Allal AS, Maire D, Becker M, Dulguerov P. Feasibility and early results of accelerated radiotherapy for head and neck carcinoma in the elderly. *Cancer.* 2000; 88(3):648–652. [Epub 2000/01/29]. [PubMed: 10649260]
29. Pignon T, Horiot JC, Van den Bogaert W, Van Glabbeke M, Scalliet P. No age limit for radical radiotherapy in head and neck tumours. *Eur J Cancer.* 1996; 32A(12):2075–2081. [Epub 1996/11/01]. [PubMed: 9014748]

30. Kogashiwa Y, Nagafuji H, Kohno N. Feasibility of concurrent chemoradiotherapy with S-1 administered on alternate days for elderly patients with head and neck cancer. *Anticancer Res.* 2012; 32(9):4035–4040. [Epub 2012/09/21]. [PubMed: 22993356]
31. Tsukuda M, Ishitoya J, Mikami Y, Matsuda H, Horiuchi C, Taguchi T, et al. Analysis of feasibility and toxicity of concurrent chemoradiotherapy with S-1 for locally advanced squamous cell carcinoma of the head and neck in elderly cases and/or cases with comorbidity. *Cancer Chemother Pharmacol.* 2009; 64(5):945–952. [Epub 2009/02/17]. [PubMed: 19219603]
32. Huang SH, O'Sullivan B, Waldron J, Lockwood G, Bayley A, Kim J, et al. Patterns of care in elderly head-and-neck cancer radiation oncology patients: a single-center cohort study. *Int J Radiat Oncol Biol Phys.* 2011; 79(1):46–51. [Epub 2010/04/17]. [PubMed: 20395066]
33. Mell LK, Dignam JJ, Salama JK, Cohen EE, Polite BN, Dandekar V, et al. Predictors of competing mortality in advanced head and neck cancer. *J Clin Oncol.* 2010; 28(1):15–20. [Epub 2009/11/26]. [PubMed: 19933920]
34. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Nguyen PD, et al. Impact of swallowing therapy on aspiration rate following treatment for locally advanced head and neck cancer. *Oral Oncol.* 2007; 43(4):352–357. [Epub 2006/08/26]. [PubMed: 16931114]
35. Myers C, Kerr P, Cooke A, Bammeke F, Butler J, Lambert P. Functional outcomes after treatment of advanced oropharyngeal carcinoma with radiation or chemoradiation. *J Otolaryngol Head Neck Surg.* 2012; 41(2):108–118. [Epub 2012/05/10]. [PubMed: 22569011]
36. Salama JK, Stenson KM, Kistner EO, Mittal BB, Argiris A, Witt ME, et al. Induction chemotherapy and concurrent chemoradiotherapy for locoregionally advanced head and neck cancer: a multi-institutional phase II trial investigating three radiotherapy dose levels. *Ann Oncol.* 2008; 19(10):1787–1794. [Epub 2008/06/10]. [PubMed: 18539617]
37. Salama JK, Stenson KM, List MA, Mell LK, Maccracken E, Cohen EE, et al. Characteristics associated with swallowing changes after concurrent chemotherapy and radiotherapy in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2008; 134(10):1060–1065. [Epub 2008/10/22]. [PubMed: 18936351]
38. Locher JL, Bonner JA, Carroll WR, Caudell JJ, Kilgore ML, Ritchie CS, et al. Gastrostomy tube placement and use in patients with head and neck cancer. *Head Neck.* 2012; 34(3):422–428. [Epub 2011/05/24]. [PubMed: 21604317]
39. Kotz T, Costello R, Li Y, Posner MR. Swallowing dysfunction after chemoradiation for advanced squamous cell carcinoma of the head and neck. *Head Neck.* 2004; 26(4):365–372. [Epub 2004/04/01]. [PubMed: 15054740]
40. Nguyen NP, Frank C, Moltz CC, Vos P, Smith HJ, Karlsson U, et al. Impact of dysphagia on quality of life after treatment of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2005; 61(3):772–778. [Epub 2005/02/15]. [PubMed: 15708256]
41. Logemann JA, Rademaker AW, Pauloski BR, Lazarus CL, Mittal BB, Brockstein B, et al. Site of disease and treatment protocol as correlates of swallowing function in patients with head and neck cancer treated with chemoradiation. *Head Neck.* 2006; 28(1):64–73. [Epub 2005/11/23]. [PubMed: 16302193]
42. Cheng SS, Terrell JE, Bradford CR, Ronis DL, Fowler KE, Prince ME, et al. Variables associated with feeding tube placement in head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2006; 132(6):655–661. [Epub 2006/06/21]. [PubMed: 16785412]
43. Ebihara S, Ebihara T, Kohzuki M. Effect of aging on cough and swallowing reflexes: implications for preventing aspiration pneumonia. *Lung.* 2012; 190(1):29–33. [Epub 2011/10/29]. [PubMed: 22033612]
44. Robbins J. Normal swallowing and aging. *Semin Neurol.* 1996; 16(4):309–317. [Epub 1996/12/01]. [PubMed: 9112310]
45. Yoshikawa M, Yoshida M, Nagasaki T, Tanimoto K, Tsuga K, Akagawa Y. Influence of aging and denture use on liquid swallowing in healthy dentulous and edentulous older people. *J Am Geriatr Soc.* 2006; 54(3):444–449. [Epub 2006/03/23]. [PubMed: 16551311]
46. Lalami Y, de Castro G Jr, Bernard-Marty C, Awada A. Management of head and neck cancer in elderly patients. *Drugs Aging.* 2009; 26(7):571–583. [Epub 2009/08/07]. [PubMed: 19655824]

47. Bernardi D, Barzan L, Franchin G, Cinelli R, Balestreri L, Tirelli U, et al. Treatment of head and neck cancer in elderly patients: state of the art and guidelines. *Crit Rev Oncol Hematol*. 2005; 53(1):71–80. [Epub 2004/12/21]. [PubMed: 15607935]
48. Lin LL, Hahn SM. Combined modality therapy in the elderly population. *Curr Treat Options Oncol*. 2009; 10(3–4):195–204. [Epub 2009/06/10]. [PubMed: 19507038]
49. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, Defelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer*. 2012; 118:3377–3386. [Epub 2011/11/11]. [PubMed: 22072065]
50. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol*. 2011; 29(25): 3457–3465. [Epub 2011/08/04]. [PubMed: 21810685]

Table 1

Patient characteristics.

Age	N (%) ^a	Primary site	N (%)
0–74	35 (39)	Oropharynx	39 (44)
75–79	30 (34)	Oral cavity	33 (37)
80–84	13 (15)	Hypopharynx	15 (17)
85+	11 (12)	Larynx	2 (2)
Gender		Stage	
Female	37 (42)	II	11 (12)
Male	52 (58)	III	14 (16)
		IVA/B	63 (71)
Race/Ethnicity		CRT regimen	
Caucasian	46 (52)	FHX	34 (38)
African-American	23 (26)	Paclitaxel + FHX	26 (29)
Asian	2 (2)	Irinotecan + FHX	7 (8)
Latino	2 (2)	Cetuximab + FHX	6 (7)
Unknown	16 (18)	Bevacizumab + FHX	3 (3)
		Docetaxel + FHX	2 (2)
		Other (non-FHX-based)	11 (12)
ECOG performance status		Induction chemotherapy	
0	16 (18)	Yes	20 (22)
1	22 (25)	No	67 (75)
2	5 (6)	Unknown	2 (2)
3	2 (2)		
Unknown	44 (49)		
Charlson comorbidity index ^b		Twice-daily radiation	
0	26 (29)	Yes	42 (47)
1	23 (26)	No	39 (44)
2	27 (30)	Unknown	8 (9)
3+	13 (15)		

Abbreviations: CRT = chemoradiation therapy; FHX = 5-fluorouracil-hydroxyurea-radiation therapy; ECOG = Eastern Cooperative Oncology Group.

^aPercentage totals may not add up to 100% due to rounding of values.

^bExcluding diagnosis of cancer.

Table 2

Swallowing function and gastrostomy tube utilization.

Gastrostomy tube	N (% total)	Mean time to placement from CRT initiation	Median time to placement from CRT initiation
Placement pre-CRT	13 (15)	–	–
Placement during CRT	42 (47)	9.6 days	17.5 days
Swallowing function			N (%)
Aspiration present at baseline evaluation ^a			20 (29)
Aspiration developing post-CRT ^b			19 (41)
Aspiration persisting at 6 months post-CRT ^c			10 (91)

Abbreviations: CRT = chemoradiation therapy.

^aOnly 70 patients had baseline swallowing evaluation documented.^bOnly 46 patients had baseline and at least one post-CRT (within 1 month) swallowing evaluations documented.^cOnly 11 patients had serial swallowing evaluations documented up to 6 months post-CRT.

Table 3

Summary of select prior studies of younger and older adults with LA-HNC undergoing concurrent CRT.

Study	N	Median age (years)	PS	IC	CRT regimen	CRT completion rate	OS	Grades 3–4 hematologic toxicity (overall)	Gastrostomy tube placement rate
Aitoldi et al. ¹³	40	73.5	ECOG PS 2 = 5%	None	Carboplatin/RT* (52–62 Gy) not twice daily	80%	3-year: 64%	25%	Unknown
Boscolo-Rizzo et al. ¹⁴	44	71	All KPS 60%	Cis + 5-FU × 1 cycle	Cis + 5-FU/RT (66–70 Gy) not twice daily	84%	3-year: 31%	45%	66%
Michal et al. ¹⁵	44	72	All ECOG PS 0–1	None reported	Cis + 5FU/RT** (68–74 Gy) 30% twice daily	82%	5-year: 49%	Neutropenia: 80% neutropenic fever: 64% thrombocytopenia: 25%	89%

Abbreviations: 5-FU: 5-Fluorouracil; Cis: cisplatin; CRT: chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; IC: induction chemotherapy; KPS: Karnofsky performance status; LAHNC: locally advanced head/neck cancer; OS: overall survival; PS: performance status; and RT: radiotherapy.

* All patients received primary surgical resection.

** Some patients (N = 3) received gefitinib in addition as part of the clinical study.