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Radiation therapy is well tolerated and produces excellent control rates in elderly patients with locally advanced head and neck cancers

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Author contributions

1. All authors of this research paper have directly participated in the planning, execution, or analysis of this study.
2. All authors of this paper have read and approved the final version submitted.

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Abstract

Purpose—Management of locally advanced head and neck cancer (LAHNC) in the elderly is challenging due to multiple co-morbidities, poor organ function and performance status. The aim of this study was to evaluate efficacy of radiation therapy (RT) in elderly patients, defined as 65 years and older, with high-risk LAHNC.

Materials and Methods—An IRB approved retrospective chart review of elderly patients was performed, of whom 73 patients were selected for analysis. The stages included were II/III-IV. Sites included were oropharynx, oral cavity, larynx, salivary gland, nasopharynx, nasal cavity, paranasal sinus, hypopharynx and unknown primary.

Results—Median age was 74 years. Thirty nine (53%) patients received concurrent chemotherapy. Median time to completion of RT was 53 days. Median external beam radiotherapy (EBRT) dose was 66 Gy. With a median follow-up of 24 months, overall local control (LC) was 80% and distant metastasis (DM) was 12%. Sixty patients (82%) were alive at the time of study. Two-year overall survival (OS) was 96% (95% CI=87%, 99%). Chemotherapy did not improve LC [80% (chemo) vs 79% (no chemo), $p=0.88$] or DM [11% (chemo) vs 14% (no chemo), $p=0.73$]. Interestingly, patients receiving RT using intensity-modulated radiation therapy (IMRT) had a significantly higher rate of LC vs three-dimensional conformal radiotherapy (3DCRT) (94% vs 68%, respectively, $p=0.008$). Grade 2/3 toxicity was seen in 70/73 (96%) patients while grade 4 toxicity was seen in three patients (4%).

Conclusion—Elderly patients with LAHNC have high rates of LC and OS. Prospective studies can reveal more insight into this increasingly important clinical problem in elderly patients.

Keywords

elderly; IMRT; Head and Neck; radiation; 3D

Introduction

Radiotherapy (RT) is one of the most important treatment modalities for head and neck cancers (HNC) either as a primary treatment or combined with surgery and chemotherapy. Over the past 20 years, RT technology has advanced from 2D (2-dimensional) to 3D, IMRT (intensity-modulated radiation therapy) and SRT (stereotactic radiation therapy). With advancement in technology, RT has become highly conformal and dose-escalation is being achieved to the tumor while reducing normal tissue doses. However, RT is still associated with considerable acute and long-term toxicity especially when combined with chemotherapy (1). The most common reason involves the more frequent use of concurrent chemotherapy with RT both primarily and post-operatively based on a number of randomized trials that showed benefit with this treatment (2) versus no chemotherapy or sequential therapy used previously. Another theoretical risk may be a more spread out low RT dose using IMRT versus 3D.

About 54% of all head and neck cancers comprising of laryngeal, oral cavity and pharyngeal carcinomas present in patients over the age of 65 (3). Management of this cancer in the elderly age group is very challenging due to co-morbidities, poor organ function status and poor performance status of such patients (4). Since the elderly are often underrepresented in clinical trials (Table 1) (5–11), the optimal treatment for such aggressive cancers in the elderly is not clear. We wanted to study the outcomes of elderly patients with LAHNC treated with RT.

Materials and Methods

An IRB approved retrospective study was done on patients aged 65 and above who were treated for LAHNC at Weill Cornell Medical Center between 2000–2010. A total of 73 patients with American Joint Committee on Cancer (AJCC, 6thed) Stage II–IVC (stage II had high risk features and stage IVC had a single site of metastasis that was resected) were selected. A total of 155 patients out of 441 patients treated in the department during this time were 65 years and above, treated consecutively at our institution, and were selected based on risk factors (mentioned below). Of these, 73 with adequate documentation and follow-up were analyzed; the remaining 82 were excluded from the review if they lacked proper documentation regarding treatment (e.g., radiation dose and/or fractional dose and/or techniques and/or lacked follow-up, chemotherapy details, etc.). Patient characteristics are shown in Table 2. Patients were selected for definitive chemoradiation (CRT) vs surgery followed by CRT based on the decision made in a multidisciplinary conference as well as patient preference. Patients were selected for post-operative RT if they had other high risk features, e.g. nodal involvement, T3–T4 disease, positive margins or extracapsular extension (ECE) after surgical resection. Majority of patients had squamous cell cancers although a select group of patients had histology such as plasmacytoma or melanoma (Table 3). The latter group of patients were selected for analysis since RT dose and fields for such tumor types are similar to other locally advanced HN cancers and patients are at similar risk of acute and chronic toxicity. Patient treatment characteristics are shown in Table 4. Radiation therapy was delivered using 3-D conformal technique (3D) or IMRT (Intensity Modulated Radiation Therapy) depending on patient's set up and availability of technology, e.g. patients with advanced neck disease where parotids would not have been spared by IMRT were treated with 3D. Most patients treated after 2005 were treated with IMRT. Majority of patients treated with IMRT were treated with extended neck field technique. For stage III/IV patients treated definitively with RT, chemotherapy was used with RT unless contraindicated due to patient's co-morbidities or patient refusal. The use of feeding tube (PEG) during treatment was at the discretion of the treating physician. Our policy is to recommend placement of PEG prior to beginning CRT. However, PEG is not recommended if RT alone is being given or if the patient refuses. Two patients received brachytherapy as a part of the definitive treatment for residual disease. Brachytherapy was delivered using HDR (high dose rate) technique using flexiguide catheters (Best inc.) and given BID (twice a day). Side effects were graded using the Radiation Therapy Oncology Group (RTOG) toxicity grading criteria (Grade 1-mild, 2-moderate, 3-severe, 4-permanent damage, 5-death). Overall local control (LC) was defined as no evidence of cancer recurrence in the head and neck region. Distant metastasis (DM) is defined as evidence of cancer recurrence outside the head and neck region. Overall survival (OS) was defined from treatment till the time of death.

Statistical Analysis

Descriptive statistics (including mean, standard deviation, median, range, frequency, percent) were calculated for demographic and clinical/treatment factors of interest. The two sample t-test and Wilcoxon rank-sum test were used to compare age and time to completion of RT treatment, respectively, between levels of clinical/treatment characteristics. The chi-square test or Fisher's exact test was used, as appropriate, to compare categorical clinical outcomes (i.e., LC, DM) between levels of treatment characteristics. OS for the cohort was evaluated by Kaplan-Meier survival analysis and 2-year OS was estimated along with a 95% confidence interval (95% CI) in order to assess the precision of the obtained survival estimate. Univariate cox proportional-hazards regression analysis was performed to estimate the hazard ratio (for death) associated with each one-year increase in age. All p-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were

performed in SPSS Version 18.0 (SPSS Inc., Chicago, IL) and STATA Version 11.0 (StataCorp, College Station, TX).

Results

Patient and tumor characteristics

(Tables 2, 3): Median age was 74 years (range 65–88 years). Thirty-six percent of patients were female. Most common site included was oro-pharynx (32%) followed by oral cavity (23%). Most common histology was squamous cell carcinoma (82%). Approximately 49% of patients were Stage IV (IVA, IVB, IVC).

Treatment characteristics

(Tables 4, 5): The median time to completion of RT treatment was 53 days (range 27–137 days). Thirty four (25/73) percent of patients took longer than 60 days (8 weeks) and four patients took longer than 90 days to complete RT. Mean and median external beam RT dose was 63.7 and 66 Gy (range 27–72 Gy), respectively, and 1.8 Gy or 2 Gy per fraction was used. The patient who received 27 Gy received it for recurrent oral cavity cancer after prior history of full dose CRT. Spinal cord was the dose limiting structure since a 3D plan was utilized. Forty-one percent of patients received post-operative RT for high risk disease. Forty-four percent of patients had PEG placement either before or during RT. PEG status was unknown in 16% of patients. Sixty-two percent of patients (N=45) received chemotherapy of which 87% (39/45) received concurrent chemotherapy. Most patients had a cisplatin based regimen. Forty-two percent of patients had an IMRT based RT planning.

Toxicity

All patients developed grade 2 or higher (RTOG grade) side effects, with most patients experiencing grade 2/3 side effects (96%). Most common toxicities included dermatitis, mucositis, dysphagia and xerostomia. Three patients developed grade 4 (4%) toxicities including fistula, esophageal stricture, tracheostomy dependence.

Local Control and Distant Metastasis

(Tables 6–8): With a median follow-up of 24 months (range 1–96 months), local control was 80%. Twelve percent developed distant metastasis. Eighty-two percent of patients were alive at the time of last follow-up. Two-year overall survival was 96% (95% CI = 87%–99%); however, the survival curve should be interpreted with caution given the small number of events contributing to the analysis (Figure 1). There was no correlation between age and local control ($p=0.79$). Similarly, there was no correlation between age and DM ($p=0.49$). Patients with local control had a shorter median time to completion of RT compared to those without local control (52.5 vs. 65.0 days, respectively, $p=0.02$). Use of chemotherapy did not affect DM ($p=0.73$) or LC ($p=0.88$).

Radiation technique and local control

(Table 7): Patients who received RT using IMRT showed a higher local control vs 3-D treatment planning ($p=0.008$). There was also a non-significant trend for an advantage of IMRT over 3-D planning in terms of DM ($p=0.17$). Time to completion of RT was slightly longer in patients who received chemotherapy compared to no chemotherapy (median=54.0 vs. 53.0 days, respectively, $p=0.23$) and those who received PEG compared to no PEG (median=56.5 vs. 51.0 days, respectively, $p=0.054$). Twenty-four patients (33%) had more than a 2 week treatment delay (average treatment being 7 weeks) (Table 9). Twenty patients (20/24, 83%) of those with this delay received chemotherapy and RT. Five patients took 90 or more days to complete RT. One patient's chemotherapy was changed from cisplatin

based to cetuximab after marginal renal failure. Based on univariate cox proportional hazards regression model, the hazard ratio for age and overall survival was 1.24 (increased risk of death for each one-year increase in age ($p=0.06$)).

Discussion

Our study has shown an excellent local control rate and survival of elderly patients with LAHNC treated with RT. Such a promising rate of survival in this age group where we expect comorbidities, does raise the question of referral bias. Median age of our elderly group was 74 years. The definition of elderly is controversial with some authors considering an age of 70 and above as elderly and others considering a relatively younger age group (12). Socinski et al. defined an “old patient” as one whose health status has begun to interfere with oncological decision-making guidelines (13). Therefore, decisions regarding the management of such patients are almost always challenging.

Outcomes for younger patients treated with CRT are promising despite aggressive CRT regimens (table 1). In a phase II study by Semrau et al (5), 84 patients with advanced inoperable (median age 55.6y) oropharynx (majority) and hypopharynx cancers received RT (hyperfractionated, accelerated or conventional) with carboplatin and paclitaxel. Median follow-up time was 36 months. Overall survival for all patients was 46.3% at 2 years and 35.3% after 5 years. Acute grade III/IV toxicity was present in 51.2% of patients and long term toxicity was documented in 78.6% of patients. Osteonecrosis was present in 6% of patients, permanent loss of taste in 46.4% and chronic dysphagia in 58.3%. In another study (6) performed in patients with unresectable N3 disease (mean age 55y), 109 patients were randomized to CRT versus accelerated RT. In the CRT arm, RT was 64 Gy in 5 weeks and chemotherapy was cisplatin (CDDP) and fluorouracil (5FU). After CRT, adjuvant CDDP-5FU was given in good responders. Event free survival rates were not different in the 2 arms, 31.2% in CRT vs 20% in the RT (2 years) arm ($p=0.16$). Five year overall survival rates were 19.3% and 18.3% in the CRT and RT groups respectively ($p=0.7$). A feeding tube was used in 94% of the patients in the RT-CT arm, and also in 94% of patients in the accelerated RT arm, with a mean duration of 173 days (from 18 days to 20 months) and 136 days (from 41 days to 21 months), respectively ($p = 0.39$). Six months after randomization, 42 patients were still carrying a feeding tube, 19 in the CRT arm and 23 in the RT arm. In the TAX 324 phase III study (10) comparing three cycles of TPF induction chemotherapy (docetaxel 75 mg/m², cisplatin 100 mg/m² and 5FU 1000 mg/m² per day,) with three cycles of PF (intravenous cisplatin 100 mg/m², 5FU 1000 mg/m²) in patients with stage III or IV squamous cell carcinoma of the head or neck, median age was 55 years. With a median follow-up was 72.2 months, overall survival was significantly better with TPF versus PF (hazard ratio [HR] 0.74, 95% CI 0.58–0.94), with an estimated 5-year survival of 52% in patients treated with TPF and 42% in those receiving PF. In the TPF group, 3% remained feeding tube dependent, compared with 11% in the PF group. Seven percent of patients had tracheostomies in the TPF group, versus 11% in the PF group. In summary, the studies in younger patients point to mixed tumor responses and grade III/IV toxicities depending on the tumor characteristics and treatment modalities. In comparison, our older population did quite well with a LC of 80% (24 month median follow-up) and only 3 patients (4%) developing grade 4 toxicity (1 fistula, 1 esophageal stricture and 1 tracheotomy dependence). This finding is contrary to the impression that older patients do not tolerate CRT or RT well and their control rates are consequently worse. Our finding of OS of 96% at 2 years may need to be confirmed in a prospective study since it may be attributable to a significant number (13.7%) of ‘unknown’ statuses (social security death index was not queried). In addition, a 24 month median follow-up is short in comparison to the follow-up in studies mentioned for younger patients (Table 1).

There have been several studies looking at radiation options in the elderly group. Machtay et al (14) evaluated clinical factors associated with severe late toxicity with CRT in HN cancers from 3 RTOG trials (RTOG 91–11, 97–03 and 99–14). On multivariable analysis, significant variables correlated with the development of severe late toxicity were older age (odds ratio 1.05 per year; $p=0.001$); advanced T stage (odds ratio, 3.07; $p=0.0036$); larynx/hypopharynx primary site (odds ratio, 4.17; $p=0.0041$); and neck dissection after CRT (odds ratio, 2.39; $p=0.018$).

Addition of chemotherapy to RT has been shown to improve local control and survival in head and neck cancers, but is associated with significant additional toxicity (15). In post-operative settings, addition of chemotherapy has been shown to be beneficial in some studies and of limited benefit in others (16). In the meta-analysis evaluating chemotherapy in LAHNC, there was decreasing effect of chemotherapy with age (2). However, elderly patients have generally been underrepresented in clinical trials and therefore, it's not clear if the recommendations can be applied to the elderly group. In our retrospective review, chemotherapy did not show a benefit in local control or distant metastasis although the limitations of this retrospective study are obvious. This finding should be interpreted with caution since our study was not a randomization between chemotherapy and no-chemotherapy. The differences in the groups examined may not have allowed an accurate comparison between the two groups. In addition, 83% of patients in whom there was a greater than 2 week delay in RT received chemotherapy with RT which could contribute to the lack of benefit of adding chemotherapy in this study. This finding needs to be evaluated further in a prospective setting since confirmation of this finding can have a significant impact on patient management and treatment tolerance.

Prolongation of treatment reduces local control in head and neck cancers (17) and this held true for our elderly group. Feeding tube placement has been shown to be an effective way of providing nutrition during RT in select patients (18). However, there are associated implications of placing a feeding tube including potential dependence and infection (19). Our institutional policy is to recommend prophylactic feeding tube placement in patients receiving CRT. Patients who refuse PEG or patients receiving RT alone are usually not recommended to have prophylactic PEG. In our elderly group, patients with a delay more than 2 weeks (33%) was mostly related to mucositis and dysphagia. Patients with more than a 90 day treatment was related to emergency tracheotomy (2 patients), PEG placement due to mucositis (2 patients), and mucositis (1 patient).

Our elderly group showed grade 2–3 toxicities in 96% and grade 4 toxicities in 4% of patients. There were no grade 5 toxicities (treatment-related death). This is comparable to any age group. IMRT planning improved local control in our study, although these findings need to be confirmed in a prospective study since a retrospective study may have inherent biases such as patient selection. IMRT also comes with its share of risks such as unnecessary radiation exposure from scatter leading to increased scatter doses to the esophagus especially with extended field technique thereby increasing risk of esophagitis and mucositis. Several studies have found a significant difference between 3D RT and IMRT, but no study has done a comparative analysis in the elderly. Braam et al. examined 56 patients with oropharyngeal carcinoma and found mean parotid flow ratio 6 weeks and 6 months after treatment were 41% and 64% respectively for IMRT and 11% and 18% respectively for conventional radiotherapy patients (predicting xerostomia). Also, the number of complications 6 weeks after treatment was significantly lower for IMRT patients compared to CRT patients (55% vs. 87%, respectively) (20). Daly et al. examined 107 oropharyngeal carcinoma cases treated with chemo-IMRT and found the 3-year locoregional control, overall survival and disease-free survival were 92%, 83%, and 81%, respectively. About 58% were grade 3 mucosal toxicities and 5% were grade 3 skin reactions (21). Saba

and colleagues examined 80 patients with laryngeal and pharyngeal carcinomas who underwent chemo-IMRT and found comparable 3-year overall survival and disease-free survival rates (81% and 78%, respectively) (22). IMRT (with or without chemotherapy) has given excellent overall survival and local control rates with reduced toxicity, including xerostomia.

Elderly patients with LAHNC have a high response rates to RT with excellent LC and limited toxicity. IMRT improves LC compared to 3DCRT. However, CRT was associated with similar rates of LC and DM as RT alone, raising the question whether toxicities are interfering with delivery of RT. Prospective studies can reveal more insight into this increasingly important clinical problem in elderly patients.

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References

1. Van Gestel D, Van Den Weyngaert D, Schrijvers D, Weyler J, Vermorken JB. Intensity-modulated radiotherapy in patients with head and neck cancer: a European single-centre experience. *Br J Radiol.* 2011 Apr; 84(1000):367–374. [PubMed: 21415302]
2. Pignon JP, le Maître A, Maillard E, et al. Metaanalysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 2009 Jul; 92(1):4–14. [PubMed: 19446902]
3. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol.* 2009 Jun 10; 27(17):2758–2765.
4. Genden EM, Rinaldo A, Shaha AR, et al. Treatment considerations for head and neck cancer in the elderly. *J Laryngol Otol.* 2005 Mar; 119(3):169–174.
5. Semrau R, Temming S, Preuss SF, et al. Definitive radiochemotherapy of advanced head and neck cancer with carboplatin and paclitaxel : a phase II study. *Strahlenther Onkol.* 2011 Oct; 187(10):645–650. [PubMed: 21947123]
6. Bourhis J, Lapeyre M, Tortochaux J, et al. Accelerated radiotherapy and concomitant high dose chemotherapy in non resectable stage IV locally advanced HNSCC: results of a GORTEC randomized trial. *Radiother Oncol.* 2011 Jul; 100(1):56–61. [PubMed: 21831465]
7. Dechaphunkul T, Pruegsanusak K, Sangthawan D, et al. Concurrent chemoradiotherapy with carboplatin followed by carboplatin and 5-fluorouracil in locally advanced nasopharyngeal carcinoma. *Head Neck Oncol.* Jun 5.2011;30. [PubMed: 21639934]
8. Wanebo HJ, Rathore R, Chougule P, et al. Selective organ preservation in operable locally advanced head and neck squamous cell carcinomas guided by primary site restaging biopsy: long-term results of two sequential brown university oncology group chemoradiotherapy studies. *Ann Surg Oncol.* 2011 Nov; 18(12):3479–3485. [PubMed: 21553142]
9. Rampino M, Ricardi U, Munoz F, et al. Concomitant adjuvant chemoradiotherapy with weekly low-dose cisplatin for high-risk squamous cell carcinoma of the head and neck: a phase II prospective trial. *Clin Oncol (R Coll Radiol).* 2011 Mar; 23(2):134–140. [PubMed: 21030225]
10. Lorch JH, Goloubeva O, Haddad RI, et al. TAX 324 Study Group Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. *Lancet Oncol.* 2011 Feb; 12(2):153–159. [PubMed: 21233014]
11. Merlano M, Russi E, Benasso M, et al. Cisplatin-based chemoradiation plus cetuximab in locally advanced head and neck cancer: a phase II clinical study. *Ann Oncol.* 2011 Mar; 22(3):712–717. [PubMed: 20810547]

12. Jensen AD, Bergmann ZP, Garcia-Huttenlocher H, et al. Cetuximab and radiation for primary and recurrent squamous cell carcinoma of the head and neck (SCCHN) in the elderly and multi-morbid patient: a single-centre experience. *Head Neck Oncol.* 2010 Nov 26;2:34. [PubMed: 21110844]
13. Socinski MA, Morris DE, Masters GA, et al. American College of Chest Physicians. Chemotherapeutic management of stage IV non-small cell lung cancer. *Chest.* 2003 Jan; 123(1 Suppl):226S–243S. Review. [PubMed: 12527582]
14. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, Forastiere A, Ang KK. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol.* 2008 Jul 20; 26(21):3582–3589.
15. Adelstein DJ. Oropharyngeal cancer: the role of chemotherapy. *Curr Treat Options Oncol.* 2003 Feb; 4(1):3–13.
16. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG(# 9501). *Head Neck.* 2005 Oct; 27(10):843–850. [PubMed: 16161069]
17. McCloskey SA, Jaggernauth W, Rigual NR, et al. Radiation treatment interruptions greater than one week and low hemoglobin levels (12 g/dL) are predictors of local regional failure after definitive concurrent chemotherapy and intensity-modulated radiation therapy for squamous cell carcinoma of the head and neck. *Am J Clin Oncol.* 2009 Dec; 32(6):587–591.
18. Wiggens RG, Flierman L, Goossens A, et al. Prophylactic gastrostomy placement and early tube feeding may limit loss of weight during chemoradiotherapy for advanced head and neck cancer, a preliminary study. *Clin Otolaryngol.* 2007 Oct; 32(5):384–390.
19. Chen AM, Li BQ, Lau DH, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2010 Nov 15; 78(4):1026–1032.
20. Braam PM, Terhaard CH, Roesink JM, et al. Intensity-modulated radiotherapy significantly reduces xerostomia compared with conventional radiotherapy. *Int J Radiat Oncol Biol Phys.* 2006 Nov 15; 66(4):975–980.
21. Daly ME, Le QT, Kozak MM, et al. Intensity-Modulated Radiotherapy for Oral Cavity Squamous Cell Carcinoma: Patterns of Failure and Predictors of Local Control. *Int J Radiat Oncol Biol Phys.* Jul 31. 2010
22. Saba NF, Khuri FR. Optimizing systemic therapy in squamous cell carcinoma of the head and neck with a focus on targeted agents. *Curr Opin Oncol.* 2009 May; 21(3):232–237.

Figure 1.
KM curve showing overall survival.
N=73 patients. 3 deaths (status unknown for 10 patients).
Median overall survival time = not reached.
2-year OS = 95.5% (95% CI = 86.7%, 98.5%).

Table 1

Prospective studies using chemoradiation (CRT) for advanced HN cancers. Median age in the studies has been displayed in bold.

Study	Type	Age years (range)	Treatment	local control/ PFS*	Long term Toxicity	Survival*	Comments
Semrau R et al (2011) ⁵	Phase II	Median 55.6 (34-76)	CRT	29.4% PFS at 5y	78.6%	35.3% at 5y	84 patients
Bourhis J et al (2011) ⁶	Phase III	Mean 55	CRT	19.5% EFS at 5y	18%	19.3% at 5y	109 patients
Dechaphunkul T et al (2011) ⁷	Prospective	Mean 44(22-62)	CRT	72.7% PFS at 3y	-NA-	89.7% at 3y	50 patients with NP cancer
Wanebo HJ et al (2011) ⁸	Prospective	Mean 58 (32-81)	CRT	55% DFS at 5y	3 patients	47% at 5y	65 patients
Rampino M et al (2011) ⁹	Prospective Phase II	Median 59.7 (NA)	CRT	82% at 5y	16%	63% at 5y	54 patients
Lorch JH (2011) ¹⁰	Prospective Phase III	Median 55 (38-82)	CRT	45% PFS at 5y	7% tracheos tomy	52% at 5y	501 patients
Merlano M (2011) ¹¹	Prospective Phase II	Median 56 (24-75)	CRT	38% PFS at 45m	-NA-	40% at 45m	45 patients

* Results in the better arm if both arms were CRT.

PFS: Progression-free survival; EFS: Event-free survival ; DFS: Disease-free survival

Table 2**Patient Characteristics**

Age (years)	N (%)
Median	74
Minimum	65
Maximum	88
<u>Sex</u>	
Females	26 (35.6)
Males	47 (64.4)
<u>Sites</u>	
Hypopharynx	2 (2.7)
Larynx	12 (16.4)
Nasal cavity	4 (5.5)
Nasopharynx	5 (6.8)
Oral cavity	17 (23.3)
Oropharynx	23 (31.5)
Paranasal sinus	3 (4.1)
Salivary gland	6 (8.2)
Unknown primary	1 (1.4)
<u>Stage</u>	
II/III	8 (11)
III	15 (20.5)
IV	1 (1.4)
IVA	19 (26)
IVB	15 (20.5)
IVC	1 (1.4)
Recurrent	10 (13.7)
Unknown	4 (5.5)

Table 3**Tumor characteristics (Histology)**

Tumor pathology	N (%)
Acinic cell carcinoma	1 (1.4)
Adenocarcinoma	2 (2.7)
Malignant melanoma	1 (1.4)
Mucoepidermoid carcinoma	4 (5.5)
Myoepithelial carcinoma	2 (2.7)
Plasmacytoma	1 (1.4)
Sarcomatoid carcinoma	2 (2.7)
Squamous cell carcinoma	60 (82.2)

Table 4

Treatment Characteristics

Chemo Type	N (%)
No	28 (38.4)
Yes	45 (61.6)
<u>Chemo Sequence</u>	
Adjuvant	2 (2.7)
Concurrent	39 (53.4)
Neoadjuvant/Concurrent	3 (4.1)
Unknown	1 (1.4)
<u>Chemo Type</u>	
Carboplatin/Paclitaxel	4 (5.4)
Cisplatin	9 (12.3)
Cisplatin/Cetuximab	2 (2.7)
Cisplatin/Paclitaxel	3 (4.1)
Cisplatin/Docetaxel	3 (4.1)
Cetuximab	3 (4.1)
Melphalan	1 (1.4)
Paclitaxel	1 (1.4)
Docetaxel	1 (1.4)
TPF/Cisplatin	1 (1.4)
Unknown	17 (23)
<u>RT Technique</u>	
3D	41 (56.2)
IMRT	31 (42.5)
3D/IMRT	1 (1.4)

Table 5

RT characteristics

Time to completion of RT (days)	N (%)
Mean	57.7
Median	53
Minimum	27
Maximum	137
<u>EBRT dose (Gy)</u>	
Mean	63.7
Median	66
Minimum	27
Maximum	72
<u>Brachytherapy boost</u>	
No	71 (97.3)
Yes	2 (2)
<u>Post-operative RT</u>	
No	43 (58.9)
Yes	30 (41.1)
<u>PEG</u>	
Unknown	12(16.4)
No	29 (39.7)
Yes	32(43.8)

Table 6

LC and DM in patients 65 yr and older treated with RT or CRT.

Local Control	N (%)
No	15 (20.5)
Yes	58 (79.5)
<u>Distant metastasis</u>	
No	64 (87.7)
Yes	9 (12.3)
<u>Alive at the time of study</u>	
No	3 (4.1)
Yes	60 (82.2)
Unknown	10 (13.7)

Table 7

Relationship between LC and A) Age, B) Chemotherapy, C) RT technique and D) Time to completion of RT.

Local Control	Age (y)	Chemo (%)	No Chemo	RT (%) (IMRT)	RT (%) (3-D)	RT time (days)
No	74.13	9 (20)	6 (21.4)	2 (6.3)	13 (31.7)	74.33
Yes	74.75	36 (80)	22 (78.6)	30 (93.8)	28 (68.3)	54.4
	p=0.79	p=0.88		p=0.008		p=0.08

Table 8

Relationship between DM and A) Age, B) Chemotherapy, and C) RT technique.

Distant Metastasis	Age (y)	Chemo (%)	No Chemo	RT (IMRT)	RT (%) (3-D)
No	74.82	40 (88.9)	24 (85.7)	26 (81.3)	38 (92.7)
Yes	73.22	5 (11.1)	4 (14.3)	6 (18.8)	3 (7.3)
	p=0.49	p=0.73		p=0.17	

Table 9

Causes of 2 week treatment delay (average RT treatment 7 weeks)

Cause of delay	Treatment responsible for toxicity
Dysphagia	Chemotherapy/RT
Mucositis	Chemotherapy/RT
Skin reaction	Chemotherapy/RT
Vomiting	Chemotherapy/RT
Xerostomia	RT
Emergency tracheotomy	Chemotherapy/RT
Patients decision- voluntary	-NA-