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Long-Term Neck and Shoulder Function Among Survivors of Oropharyngeal Squamous Cell Carcinoma Treated with Chemoradiation as Assessed with the Neck Dissection Impairment Index (NDII)

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Abstract

Background: Of interest is the long-term neck and shoulder Impairment of patients treated with primary chemoradiotherapy (CRT). This is important for counseling patients regarding treatment decisions when discussing primary CRT.

Methods: A cross sectional study to identify factors that contribute to neck and shoulder dysfunction in patients treated with primary CRT. We utilized the Neck Dissection Impairment Index (NDII). Eighty-seven (87) patients treated between 2003-2010, who were free of disease, responded; 24 of these 87 underwent post-CRT neck dissection. Mean interval since completion of CRT was over 5 years (62.7 months). Mean age, 63.5 years, M:F 75:12.

Results: Mean NDII score was 87.4 (SD 22.1, range 5-100). Multiple linear regression revealed worse NDII scores for patients with larger pre-CRT gross tumor nodal volume (GTVnodal), controlled for age, sex, BMI and the presence of neck dissection (p=0.02). There were significant associations with increasing GTVnodal and "low" scores for components of the NDII that assessed neck pain (p=0.02), neck stiffness (p=0.01), lifting heavy objects (p=0.02), reaching overhead (p=0.02), and ability to do work (p=0.02). Physical therapy (PT) was evaluated as an "anchor" but it was prescribed "as needed", Regression revealed participation in PT was associated with higher GTVnodal, lower BMI, presence of neck dissection, and female sex (p=0.00007).

Conclusion: GTVnodal was an independent predictor of neck and shoulder.impairment. High GTVnodal was associated with increased pain and stiffness,

and increased difficulty lifting heavy objects, reaching overhead, overall ability to perform work related tasks and was associated with participation in post treatment physical therapy.

Introduction

Neck and shoulder dysfunction (or shoulder syndrome) is a well described sequela of neck dissection and includes neck pain, decreased abduction, and scapular winging [1]. The etiology of this syndrome is disruption of the innervation to the trapezius muscle as well as generalized scaring in the surgical field. While first characterized in the context of radical neck dissection, this syndrome can occur after selective neck dissection if there is dissection of the accessory nerve, the cervical nerve rootlets or the deep neck muscles [2]. The degree of impairment can be quantified using the Neck Dissection Impairment Index (NDII), a validated, 10-item survey instrument that has been shown to be the best measure of neck and shoulder dysfunction for the head and neck cancer patient [3, 4, 5]. This instrument has shown that radiation (RT) in the adjuvant setting also contributes to neck and shoulder impairment. Neck and shoulder function have also been correlated to work status and poorer NDII scores have been anchored to negative change in work status [6].

Neck and shoulder symptoms after primary radiation (RT) or chemoradiation (CRT) can include fibrotic tissue sclerosis, muscle weakness, spasm and cervical dystonia [7]. These symptoms are the result of radiation fibrosis which have been described in a most cancer sites. Hunter and Eisbruch reported on 34 patients who developed spasms of the sternocleidomastoid muscle after undergoing intensity modulated radiation therapy (IMRT) for head and neck cancer [8]. Affected SCM muscles received on average 62.3 Gray, while unaffected SCM muscles in the same patients received on averaged 52.7 Gray. The effect of dose and volume of radiation affects the extent and severity of radiation fibrosis. The adverse effects of radiation therapy on peripheral nerves are thought to be caused by decreased vascularization and fibrosis, and potentially ongoing injury due to nerve sheath fibrosis. A model for radiation induced nerve damage in the head and neck is radiation induced brachial plexopathy [9]. In response to radiation induced brachial plexopathy, radiation treatment volumes have been modified, when possible, to reduce the radiation exposure and dose to the brachial plexus. Some nerves cannot be spared the high dose volume such as nerves to the levator scapulae and the trapezius which help support the shoulder can be affected by radiation and as a result can cause shoulder symptoms in addition to neck symptoms. The “gross treatment volume” of the neck nodes is an approximate metric for the high dose volume in the neck. Muscle fibrosis in the treatment volume can also contribute to weakness and limited range of motion [10].

Due to renewed interest in primary surgery with adjuvant radiation compared to RT or CRT for patients with oropharyngeal squamous cell carcinoma (OPSCC), the interest in various measures of QOL related to these interventions has increased. In addition, the impact of primary RT or CRT independent of neck dissection on neck and shoulder related QOL is not known. There have been numerous studies on the approaches to the measurement of radiation fibrosis including subjective assessment, skin indentation, torsion techniques, electrical impedance, ultrasound and MRI [11]. The NDII will be used to gain an understanding of neck and shoulder related QOL for patients undergoing primary RT or CRT. We hypothesize that there are quantifiable changes in neck and shoulder related QOL as measured by the NDII. An understanding of the degree and type of neck and shoulder related QOL for patients with OPSCC will inform treatment decisions and pre-treatment patient counseling.

Methods

Study Design

Cross sectional study utilizing a convenience sample of surviving patients after treatment on a uniform clinical protocol for advanced stage OPSCC with CRT to describe the effect of CRT on neck and shoulder function and identify factors associated with poorer function. This research was conducted under IRB UMCC 2001-0415.

Eligibility Criteria

The patients included in this study were included based on the diagnosis of advanced AJCC 7 stage (III,IV) OPSCC, and were treated under a uniform clinical protocol consisting of weekly concomitant carboplatin (AUC1) plus paclitaxel (30 mg/m2) and intensity modulated radiation therapy (IMRT) between 2003 and 2010 [12]. Patients were excluded if they had surgery or radiation therapy to the upper aerodigestive tract prior to presentation to our clinic, if they had a pre-existing shoulder condition (to include any history of shoulder treatment, rehabilitation, trauma or surgery), or were cognitively unable to complete to survey instrument. Radiation consisted of 70 Gray to areas of gross disease in the neck, while other at risk areas received 60-63 Gray. Neck dissection was performed after chemoradiation for persistent or recurrent neck disease. All patients were free of disease at the time the NDII was completed, and surveys were administered between May 2012-January 2013. Average patient follow-up was just over 5 years (62.7 months, range 18-114). Staging was performed in accordance with the 2010 American Joint Committee on Cancer based on clinical exam, direct laryngoscopy in the operating room and either computed tomography (CT) scan or computed tomography/positron emission tomography scan (CT/PET) scan. Updated staging based on AJCC 8 criteria is included here so that these findings can be evaluated in in relation to our current staging system.

Recruitment

142 patients met the inclusion criteria. Patients were initially mailed a recruitment packet consisting of a cover letter explaining the study, instructions for participation, a consent form, and NDII survey with additional questions. Patients that did not respond to the initial recruitment packet were contacted by telephone or at regularly scheduled clinic visits. An additional 2-3 attempts at phone contact were made before patients were considered non-responders. A total of 87 out 142 patients (61%) completed the survey. Four patients (3%) declined; 18 (13%) verbally agreed to participate but did not complete the NDII instrument; 32 (23%) could not be reached. Additionally, when survey data was incomplete, patients were contacted by phone to obtain complete information. If patients perceived a difference in neck and shoulder function on one side versus the other, they were instructed to respond to reflect their symptoms on the more severely affected side.

Population Characteristics

Baseline characteristics are shown in **Table 1.** There were 87 participants who underwent primary CRT for advanced stage OPSCC from 2003-2010; the mean interval since completion of treatment was over 5 years (62.7 months, range 18-114). The mean age was 63.5 (±9) years, with a male:female ratio of 75:12. Twenty-four of these 87 patients underwent post-CRT neck dissection. There were 13 selective neck dissections, 10 modified radical neck dissections (3 with CN IX preservation, 7 with CN IX and sternocleidomastoid preservation) and 1 radical neck dissection performed. Neck dissection was performed an average of 5 months after the completion of CRT.

Variables Under Study

Univariate data includes age, sex, body mass index (BMI), T classification (T1, T2 vs T3, T4), neck dissection and gross nodal volume (GTVnodal). GTVnodal is a measure of the volume of nodal disease in the neck and is calculated from the radiation planning neck CT. GTVnodal was measured on the right and left sides individually. Sum GTVnodal, the sum of the gross nodal volumes measured on both sides of neck (sumGTVnodal) were analyzed. We did not use N classification in the model because of the collinearity with measures of GTVnodal. The NDII is a validated, self-administered, neck and shoulder impairment instrument consisting of 10 questions [3]. These questions assess neck pain, stiffness, ability to lift light and heavy objects, ability to reach above, perform self-care, overall activity level, participate in social activities, leisure and recreation activities, and work activity over the preceding 4 weeks. Patient responses are on a 5 point Likert scale, and are transformed to a 100-point scale. Higher scores indicate higher functional status; 100 indicates no impairment, and 0 indicates maximal assessed impairment Responses reflect symptoms on the more severely affected side. The NDII total score and individual item (question) scores were evaluated.

Additional questions were included regarding the use of pain medication, physical therapy, leisure activities and work activities, as previously described [6]. To assess use of pain medication, patients were asked to report the type and frequency of pain medication use. To assess utilization and benefit of physical therapy (PT), patients were asked to report on the use of PT.

Statistical Analysis

Univariate data was tabulated. To understand the relationship between neck and shoulder dysfunction and radiation dose, the GTVnodal was divided into four categories (less than $20cm^3$; $20\ cm^3$ – less than $40\ cm^3$; $40\ cm^3$ – less than $60\ cm^3$; greater than $60\ cm^3$) and assessed the correlation to NDII score via the Spearman rank correlation test. To determine if the NDII score was predicted by a pre-specified model including GTVnodal, body mass index (BMI), sex, and age a multivariable linear regression was performed within patients with subsequent neck dissection and those without subsequent neck dissection separately. Multivariable analysis for the entire group of 87 patients was also performed including an additional categorical effect of neck dissection (yes/no). Univariate and multiple logistic regression was used to help understand what particular aspects of neck and shoulder function measured by the NDII were affected by GTVnodal. To perform the logistic regression, the NDII scores were grouped as “high” (4-5/5) or “low” (1-3/5). Statistical analysis was performed using R 3.0.1.

Results

The mean NDII score for the cohort was 87.4 (SD 22.1, range 5-100). For patients treated with CRT, the average NDII score was 90.5 (SD 19.1, range 7.5-100), compared to an average score of 79.4 (SD 27.9, range 5-100) for patients treated with CRT and subsequent neck dissection (p=0.04). The majority of patients treated with CRT alone scored well on the NDII. Fifty-two percent (33/63) of patients who underwent CRT alone had an NDII score of 100/100; nearly 75% (47/63) of patients had NDII scores above 90/100.

To understand the relationship between radiation treatment variables and NDII score, we used GTVnodal, a measure of the total volume of radiographically evident disease in the neck. When examining the entire cohort, there was an association between high GTVnodal and worse NDII scores, assessed with a Spearman rank correlation test (**Figure 1**, correlation coefficient -0.22, p=0.045). This association was present even when controlling for the presence of neck dissection (**Table 2**).

Since patients who underwent neck dissection reported lower NDII scores, we sought to understand the relationship between GTV nodal and neck dissection. Therefore, multiple linear regression was performed using NDII score as the dependent variable, and included age, sex, BMI, and neck dissection as independent variables, as these have been shown to impact NDII score in our previous work [3]. When controlling for age, sex, BMI and neck dissection, the overall regression model was predictive of NDII score (p=0.009; multiple r^2=0.124). In this multiple regression analysis, both high GTVnodal p=0.02 and female sex p=0.02 were significant predictors of worse NDII score (**Table 2**). Neck Dissection was important to the model but was not significant.

A regression model was constructed to understand patient participation in PT to help understand the need for rehabilitation. The independent variables included GTVnodal, age, sex, BMI, and neck dissection, and the dependent variable was physical therapy. In our population, physical therapy was prescribed "as needed" based on patient symptoms at routine clinical follow-up. Factors that could affect the referral to PT were not included in the model such as provider follow up, socioeconomic factors and availability of PT. The overall model was highly significant (p=0.00007). Higher GTVnodal (coefficient 0.04, p=0.005), lower BMI (coefficient -0.15, p=0.03), presence of neck dissection (coefficient 1.88, p=0.02), and female sex (coefficient 2.4, p=0.01) were predictive of patients receiving physical therapy.

To help understand the components of the NDII that were scored more poorly by patients who were treated for higher GTVnodal, multiple logistic regressions were performed on each of the component scores (**Table 3**). Individual NDII item scores were defined as "good" (scores of 5/5 or 4/5) or "poor" (3/5 and lower). Variables included in the model were GTVnodal, neck dissection, sex, and BMI. The regression model showed correlation with 4 of the 10 items on the NDII. After controlling for neck dissection, sex, and BMI, patients with higher GTVnodal were more likely to have neck pain (HR: 1.22, 95%CI [1.00, 1.47]), inability to lift heavy objects (HR: 1.29, 95%CI [1.04, 1.60]), inability to reach overhead (HR: 1.39, 95%CI [1.06, 1.80]), and inability to perform work activities (HR: 1.43, 95%CI [1.08, 1.89]).

Discussion

Treatment options for advanced stage OPSCC include primary CRT with possible salvage neck dissection or primary surgery with possible adjuvant radiation or adjuvant CRT. Though these modalities have not been compared directly in a prospective, randomized controlled trial, the available evidence suggests that oncologic outcomes are similar [13, 14, 15, 16]. Treatment decisions for these patients are heavily influenced by clinician expertise and experience, with an increasing interest in limiting functional impairment associated with treatment [17]. This study uses the NDII to describe long term neck and shoulder impairment in a CRT cohort.

We found that after primary CRT, the majority of patients reported minimal neck and shoulder impairment. In our prior work evaluating primary neck dissection followed by adjuvant treatment, we showed increased shoulder and neck impairment after modified radical neck dissection. Adjuvant radiation also increased neck and shoulder impairment [3, 6, 18]. A direct comparison of this earlier work and this current study is not possible because the cohorts do not match with respect to site and stage of disease. However, this study shows that patients requiring CRT experience less neck and shoulder impairment compared to patients requiring CRT and salvage surgery This preliminary data may be helpful for counseling patients with OPSCC regarding neck and shoulder impairment after CRT with complete response or if they need a salvage neck dissection for residual disease after CRT.

The association of high GTVnodal with poorer NDII scores is a clinically useful and previously undocumented finding. For patients in this study, gross nodal disease was treated with 70 Gray of radiation, while grossly uninvolved but “at risk” areas of the neck were treated with 60-63 Gray. In patients with high GTVnodal, a larger volume of the neck is treated with 70 Gy. We postulate that treating a larger volume with 70 Gy would lead to a larger zone of fibrosis, particularly muscle fibrosis which would presumably lead to diminished mobility and innervation. This relative weakness results in inflammation from overuse of the remaining muscle units. The relationship with GTV opens opportunities for sparing of paravertebral muscles with the hope of decreasing neck and shoulder morbidity [8]. High GTVnodal could also be associated with a degree of radiation related brachial plexopathy that could lower NDII scores, however; radiation plans with IMRT (all the patients were treated with IMRT) are designed to avoid the brachial plexus as much as is possible. In addition, the effect of brachial plexopathy would not be limited to the shoulder girdle but also affect the ipsilateral limb.

In multiple regression analysis of individual NDII component questions, we found that GTVnodal was a significant predictor of poor scores in items assessing neck pain, ability to reach overhead, ability to lift heavy objects, and overall work ability. It is possible that the observed association between increased neck and shoulder impairment and GTVnodal is due entirely to tissue changes in the neck, but we believe that there is also increased nerve damage with increased GTVnodal. Difficulty with reaching overhead is directly attributable to impaired spinal accessory nerve function, and was seen in this cohort. However, an association between GTVnodal and neck stiffness was not observed, suggesting stiffness alone is not predicted by nodal volume.

To understand if the neck and shoulder impairment was significant to clinicians, we used PT as an “anchor” but it was prescribed “as needed” based on patient symptoms during routine clinical follow-up. Of course, participation in PT is not an objective marker of the degree of impairment. There are many factors that relate to a participation in PT that include but are limited to: the clinician following the patient and their ability to understand if a referral is appropriate, whether a patient's life obligations relating to work or family allow them to attend PT visits, socioeconomic factors that affect participation in PT, and patient motivation. The regression model for patients who self-declared participation in PT was significant and suggested that high GTV nodal "anchored" rehabilitation. Prior work relates neck and shoulder impairment to decreased work and leisure activities [6]. This study shows that GTV nodal, in addition to neck dissection, lower BMI and female sex is associated with greater likelihood of a PT participation It is notable that we did not use variables related to socioeconomic status, insurance coverage, availability of PT or other factors that could affect the ability of patients to participate in PT.

There a several limitations: 1) This data is from a cohort of OPSCC patients who underwent CRT with carboplatin and paclitaxel. Outcomes from patients who were treated with radiation alone or CRT with cisplatin would be interesting to compare to the findings in this cohort. 2) The rate of neck dissection was higher in this cohort than would be observed in a more contemporaneous cohort. Recent reports have shown that neck dissection rates can be as low as 5% if PET scans are performed at 16 weeks [19]. 3) The response rate for completion of the NDII was 61%, Although this response rate is acceptable, there is concern with respect to response bias particularly if the bias is related to the patient's neck and shoulder related quality of life. 4) With respect to the use of the NDII as the survey instrument. The NDII is not the most widely utilized assessment of shoulder function but it is specifically designed for the post treatment head and neck cancer patient. It was validated in a cohort of patients who had undergone neck dissection and there is clear evidence that the NDII has shown a statistically significant outcome with respect to the effect of radiation on neck and shoulder function. 5) The NDII is structured to query neck and shoulder together. This design originates from the initial validation. Patient who had undergone neck treatment had better metrics with respect to validation if “neck and shoulder” were used together in the question relating to their impairment related to their neck treatment.

Overall, this study contributes to our understanding of the impact of treatment choices for advanced OPSCC by defining the morbidity of primary CRT to the neck among long term survivors. We have identified high GTVnodal as a predictor of increased neck and shoulder impairment.

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Table 1. Population Characteristics

Demographics	Number of Patients=87
Sex:	
Male Female	75 12
Average Age (range):	63.5 (40-85)
Average BMI (range):	29.0 (16-55)
P16 Status:	
Positive Negative Unknown	77 6 4
T stage:	
1 2 3 4	16 36 15 20
N stage AJCC 7:	
N0 N1 N2a N2b N2c N3	5 9 7 41 17 8
N stage AJCC 8:	
N0 N1 N2 N3	5 48 16 8
Gross nodal volume measures	
sumGTVnodal maxGTVnodal	31.2 cc^3 range: 0-158.7 cc 30.3 cc^3 range: 0-158.7 cc
Average Time from CRT to Survey completion:	62.7 months (18-114)

NDII score	87.4 (22.3) range: 5-100

Table 2. Multiple linear regression to estimate NDII score. The model was predictive of NDII score (overall p = 0.0092, adjusted R^2 = 0.124).

Coefficient	**Estimate (SE)**	**P-value**
Intercept	107.05 (20.70)	$< 1 \times 10^{-5}$
GTVnodal (each $1cc^3$)	-0.21 (0.09)	**0.024**
BMI (each increase of 1)	0.28 (0.41)	0.503
Nodal dissection	-9.76 (5.44)	0.077
Female sex	-16.19 (6.88)	**0.021**
Age (each year)	-0.26 (0.28)	0.354

Table 3. Multiple Logistic Regression Analysis of Component NDII "low" scores with GTVnodal, neck dissection (yes vs no), BMI, Sex (female). Each row is a separate model containing all four potential predictors; Odds ratio are the odds of reporting "low" score on the component question in each row.

NDII Question	GTVnodal		Neck Dissection		Sex (Female)		BMI		
	OR	p	OR	p	OR	p	OR	p	model p-value
Neck Pain	**1.22 (1.00, 1.47)**	**0.05**	**3.31 (1.07, 10.27)**	**0.04**	**2.63 (0.60, 11.58)**	**0.20**	**1.01 (0.92, 1.11)**	**0.78**	**0.03**
Stiffness	1.28(1.04, 1.57)	0.02	1.53 (0.45, 5.21)	0.50	2.17 (0.45, 10.39)	0.33	1.00 (0.90, 1.11)	1.00	0.10
Self-Care	1.15 (0.81, 1.62)	0.44	4.36 (0.60, 31.76)	0.15	11.57 (1.43, 93.39)	0.02	0.91 (0.76, 1.10)	0.34	0.08
Lift Light Objects	1.13 (0.83, 1.53)	0.45	1.68 (0.25, 11.39)	0.59	8.80 (1.32, 58.64)	0.02	0.97 (0.81, 1.15)	0.71	0.23
Lift Heavy Objects	**1.29 (1.04, 1.60)**	**0.02**	**4.61 (1.23, 17.23)**	**0.02**	**6.04 (1.15, 31.86)**	**0.03**	**1.01 (0.91, 1.12)**	**0.86**	**0.005**
Reach Overhead	**1.39 (1.06, 1.80)**	**0.01**	**2.52 (0.59, 10.74)**	**0.21**	**4.34 (0.79, 23.97)**	**0.09**	**0.92 (0.80, 1.05)**	**0.22**	**0.02**
Overall Activity	1.07 (0.83, 1.39)	0.58	2.59 (0.60, 11.15)	0.20	1.61 (0.26, 9.86)	0.61	0.90 (0.78, 1.05)	0.17	0.26
Social Activity	1.19 (0.91, 1.54)	0.20	3.59 (0.70, 18.31)	0.12	7.25 (1.17, 44.73)	0.03	0.98 ().86, 1.13)	0.82	0.12
Leisure Activity	1.14 (0.89, 1.45)	0.31	3.21 (0.75, 13.78)	0.12	3.93 (0.73, 21.05)	0.11	0.93 (0.82, 1.07)	0.32	0.16
Work	**1.43 (1.08, 1.89)**	**0.01**	**2.75 (0.54, 13.85)**	**0.22**	**7.19 (1.13, 45.71)**	**0.04**	**0.93 (0.81, 1.08)**	**0.35**	**0.02**