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The Relationship between Age, Comorbidities and Complications in Head and Neck Cancer Patients undergoing Curative Surgery

Short title: Comorbidities in Head and Neck Surgery

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Abstract word count: 148

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Abstract and Key Words

Background: both age and comorbidity are accepted as significant prognostic factors for adverse peri-operative outcomes in major surgery. Elderly patients may be overlooked for radical treatment for fear of poor peri-operative outcome. We aim to assess the relationship between age, comorbidities and post-operative outcomes in a tertiary head and neck unit.

Methods: a retrospective analysis was undertaken on 651 patients who underwent surgery for head and neck cancer at a tertiary hospital between 2007 and 2014.

Results: two hundred and fifty-three (38.9%) patients were aged ≥ 70 years old and 398 (61.1%) patients were ≤ 69 . Age alone did not predict prolonged post-operative stay, peri-operative complications nor peri-operative mortality. Congestive cardiac failure and/or complicated diabetes were significantly associated with poor outcomes, as was male sex.

Conclusion: Patients of any age with cardiac failure or complicated diabetes have a higher rate of post-operative complications in head and neck surgery.

Word count: 148

Key Words: age, comorbidities, complications, peri-operative, head and neck cancer.

Main Text

Introduction

The mainstay of curative head and neck cancer treatment remains radical surgery and radiotherapy. Head and neck cancer is predominantly a disease of the elderly and clinicians are often faced with the difficult decision about whether to de-escalate radical treatment in increasingly elderly patients. Tertiary referral centres particularly concentrate on elderly patients and locally advanced tumours. Patients not considered for radical treatment usually face a rapid decline with difficult to manage local symptoms including pain, dysphagia, dysarthria, bleeding and progressive external deformity.

Several studies suggest that age alone does not predict peri-operative risk in head and neck cancer patients ^(1, 2). In contrast, several studies have found a correlation between increased age and poor post-operative outcomes ^(3, 4). Pre-existing comorbidities have also been found to predict complications after head and neck cancer surgery ^(5, 6).

However, a recent study by Bertelsen *et al* found that neither age nor comorbidities contributed to complications for craniofacial malignancies. Hence, the question remains whether age or comorbidities are the principal factor clinicians should use in estimating peri-operative risk related to major head and neck cancer surgery.

We investigated whether age or comorbidities predicted poor peri-operative outcomes in patients considered for curative surgery in a tertiary head and neck unit. We hypothesize that age alone is not a prognostic factor in all head and neck cancer patients. Increasing age is often associated with significant comorbidity, which are confounders leading us to believe age is a negative prognostic factor. In this paper, we divide patients into two groups by age and control for comorbidity to investigate their impact on peri-operative outcomes.

Materials and Methods

The study was undertaken with the understanding and informed consent of each patient according to ethical principles. Ethics approval was obtained from the Melbourne Health Human Research and Ethics Committee for this study. A retrospective cohort study on head and neck cancer patients (including malignancies of the lip, oral cavity, oropharynx, hypopharynx, larynx, nasal cavity and sinus, salivary gland, and skin overlying the head and neck region) that presented to The Royal Melbourne Hospital, a tertiary referral centre between January 2007 and September 2014 was conducted. All cases were discussed at a multidisciplinary meeting and referred for medical

optimisation if required prior to surgery. More frail and poorly functioning elderly patients (ECOG 4) considered unfit for curative treatment were not evaluated. Surgeries included those for the primary lesion (oral resection, buccal mucosal resection, floor of mouth resection, cheek resection, tongue resection, orbital exenteration, intranasal ethmoidectomy, rhinectomy, maxillectomy, lateral temporal bone resection, parotidectomy, mandibulectomy, submandibular gland resection, vermillionectomy, wedge excision of lip, thyroidectomy, skin excision, laryngectomy, pharyngectomy, vocal cord resection, skull base procedure), for the neck (neck dissection), reconstruction, and utility operations (tracheostomy and extraction of teeth).

Patient, tumour and surgical procedure information was identified from the Head and Neck Tumour Stream Database (ACCORD) and checked against coding data and the medical record. Patients with recurrent malignancy or a second primary malignancy in the head and neck region were excluded. Patients were separated into two groups according to age < 70 or ≥ 70 years old (Table 1).

Direct logistic regression was performed to assess the impact of a number of pre-operative factors on the likelihood that a patient would experience a post-operative complication (either one or more of a fistulae, infection, pneumonia, pressure injury, venous thrombosis, thromboembolic event, post-operative AMI, chyle leak, delayed decannulation, delayed healing, flap complication, haemorrhage, necrosis, nerve palsy,

pneumothorax or unplanned return to theatre). The logistic regression model contained eight independent variables (age, sex, diabetes without known complications, diabetes with known complications, renal failure, congestive cardiac failure, chronic obstructive pulmonary disease and dementia). Complicated diabetes included those diabetic patients with cerebrovascular, cardiovascular or peripheral vascular disease or diabetic retinopathy, neuropathy and nephropathy.

Results

Six hundred and fifty-one patients (62.8% male) were surgically treated for head and neck cancer between January 2007 and September 2014. There were 398 patients younger than 70 and 253 older than or equal to 70.

Diabetes with complications ($p=0.02$), current or smoking history ($p=0.000$), renal failure ($p=0.027$) and congestive cardiac failure ($p=0.007$) were significantly more common in the older population (Table 1). Younger patients were more likely to have mucosal resection ($p=0.000$), complex reconstruction ($p=0.001$) and inpatient post-operative death ($p=0.03$). Patients over 70 years old were more likely to develop post-operative haemorrhage ($p = 0.007$).

The result of our data analysis containing all predictors was statistically significant, χ^2 (9, n=651) = 49.89, $p < .001$, indicating that the logistic regression model was able to distinguish between patients who recorded and did not record a post-operative complication. These results explained between 7.7% (Cox and Snell R Square) and 11.0% (Nagelkerke R Squared) of the variance in post-operative complications recorded, and correctly classified 74.4% of cases.

Three independent variables made a unique statistically significant contribution to the model (sex, diabetes with known complications, and congestive cardiac failure) (Table 2). The strongest predictor of experiencing a post-operative complication was congestive cardiac failure (OR of 14.52, 95% CI 3.82 to 55.17, $p < 0.001$).

The second strongest predictor of experiencing a post-operative complication was diabetes with known complications (OR of 14.43, 95% CI 3.37 to 61.49, $p < 0.001$).

Finally, males were 1.64 times more likely to experience a post-operative complication than females (95% CI 1.11 to 2.41, $p = 0.013$).

Discussion

Elderly patients often receive different treatment compared with their younger counterparts for head and neck malignancies, being offered less extensive surgery or no surgery at all, for fear of post-operative morbidity and mortality^(8,9). Patients not considered for radical treatment have grim prospects of rapidly advancing and locally destructive tumour growth. This series of 651 head and neck cancer patients treated surgically in a tertiary referral head and neck centre found that age alone did not predict poor peri-operative outcomes. Instead, comorbidities, particularly congestive cardiac failure, complicated diabetes and male gender were independently predictive of poor peri-operative outcomes.

Age alone did not predict poor peri-operative outcomes for patients deemed fit for surgery. Several papers have previously shown that advanced age alone does not result in poorer peri-operative outcomes for patients, although several were of small sample size or only measured complications that required surgical intervention^(1, 2, 7, 10).

Comorbidities seem to be more predictive of poor peri-operative outcomes following head and neck cancer surgery. Genther *et al* performed a retrospective analysis on 61,740 elderly patients who received surgical intervention for head and neck cancer. Patients were separated into groups based on the severity of their comorbidity, and those with a higher class had worse hospital outcomes⁽³⁾. Sanabria *et al* also found that elderly patients undergoing any treatment for head and neck malignancies have

increased overall mortality if they have advanced pre-existing comorbidity ⁽¹¹⁾. Goh *et al* investigated outcomes for head and neck malignancy post free flap reconstruction and similarly found that comorbidity, rather than age, predicted post-operative complications ⁽¹²⁾. Our findings agree with these, with the added information that some specific comorbidities have a greater influence on post-operative outcomes. Hence, we suggest that instead of assessing age, we should instead focus our attention on comorbidity.

We found congestive cardiac failure to be the strongest predictor for post-operative complication in all patients. These patients were over 14 times more likely to have a post-operative complication. Little research currently exists investigating the impact congestive cardiac failure has on post-operative outcome. Piccirillo *et al* showed that the five-year survival of head and neck squamous cell carcinoma patients with congestive heart disease was significantly worsened, while Kravchenko *et al* showed significantly increased peri-operative mortality in lung cancer patients with congestive cardiac disease ^(13, 14).

Diabetes with complications was the second strongest comorbidity which has a major detrimental impact on outcome (OR 14.43). Raikundalia *et al* found that these patients had higher rates of post-operative infection, pulmonary oedema, respiratory failure, acute renal failure, urinary tract infection and cardiac events ⁽¹⁵⁾. Additionally, both Liu

et al and Joo *et al* found that elderly patients with diabetes had increased risk of free flap complications post tumour resection ^(16, 17).

There was an overall increased number of post-operative complications seen in the younger population compared to the older population (29.1% versus 28.5% respectively), although this was insignificant. This could be explained by the greater percentage of total comorbidities (29.9% versus 27.3%), or larger number of complex flap reconstructions (50.3% versus 36.4%). Of the 200 younger patients that received a flap reconstruction, 23 experienced a flap complication (11.5%). This compare with 7 of 92 older patients (7.6%). This could be due to earlier mobilisation and attempts at upgrading diet. As a result, the younger populating has a higher number of delayed decannulations. However, despite this, the younger population stayed a mean 2.6 days less in hospital. This could be explained by the increased physiological reserve in the younger population and the psychosocial challenges that accompany caring for the elderly including placement issues and rehabilitation requirements. Causes of prolonged length of stay (> 60 days) included fistula formation, haemorrhage, flap or wound infection, pneumonia and return to theatre.

There were also more inpatient deaths in the older population (8 versus 1, p value 0.003). On review of files, it was found that most of the older population patients presented with advanced T4 disease, had extensive pre-existing chronic comorbidities

and endured many post-operative complications prior to death (> 7 complications). Two patients had diabetes with complications, one patient had NYHA class 3 congestive cardiac failure, and one patient with chronic renal failure. L'Esperence *et al* similarly found increased 90-day mortality in patients with large extent of resection, age >90 and severe comorbid disease ⁽⁴⁾. There was an overall smaller proportion of T4 disease present in the older population, which could be attributable to patients requests for non-operative management due to prolonged recovery and impact on quality of life. In comparison, a greater proportion of the older population presented with T0 disease compared to the younger population. This could be due to the close relationship some elderly patients have with their primary care physicians and early detection of abnormalities.

A lower proportion of older patients were treated with mucosal resections, neck dissections and complex reconstructions than compared to the younger population. This could again be due to patient preference for non-operative management or a combined multidisciplinary team opinion that anaesthetic risk and poor functional status would deem the patient a poor operative candidate.

Although the sex ratios are similar in both the younger and older groups, as expected there are fewer males in the older group, presumably due to the health benefits of being

female with regards to long life. Thus, the higher complication rate seen in the younger group, could be due to the larger proportion of males.

Limitations of this study include its retrospective nature and the potential for inaccurate data collection (addressed by seeking multiple sources of data on peri-operative outcomes). The department policy is that patients are considered for radical treatment by functional status and anaesthetic risk rather than biological age. The basic tenet that comorbidity rather than age predicts perioperative risk in head and neck cancer treatment remains. However, our study has not included those patients who presented for care and were offered palliation, declined referral to a tertiary centre, or did not present to their general practitioner to get a referral for management, nor what their comorbidities or age were. The future direction of this paper is to investigate the long-term outcomes, including adjuvant radiotherapy and chemotherapy

Conclusion

This study aids in selection of head and neck cancer patients for surgery that includes functional and anaesthetic risk, rather than age. Our study suggests that age alone is not a limiting factor for surgery, and that comorbidities should be taken into consideration. Patients with congestive cardiac failure and/or complicated diabetes have a high rate of peri-operative complications following head and neck cancer surgery.

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Disclosures

Nil disclosures to declare

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TABLE 1

Table 1. Demographics of all subjects.

	Younger (<70yrs)	Older ($\geq$ 70yrs)	P-value	All Subjects
n	398	253	-	651
Age				
Median (Range)	58 (18-69)	79.0 (70-95)	-	65.5 (18-95)
Sex			0.247***	
Male	257 (64.6%)	152 (60.1%)	-	409 (62.8%)
Female	141 (35.4%)	101 (39.9%)	-	242 (37.2%)
Prevalence of Smoking	109 (27.4%)	19 (7.5%)	0.000*	128 (19.7%)
Comorbidities				
Any Comorbidity	119 (29.9%)	69 (27.3%)	0.527*	188 (28.9%)
Diabetes without Complications	20 (5.0%)	21 (8.3%)	0.131*	41 (6.3%)
Diabetes with Complications	3 (0.8%)	12 (4.7%)	0.02*	15 (2.3%)
Renal Failure	6 (1.5%)	12 (4.7%)	0.027*	18 (2.8%)
CCF	5 (1.3%)	13 (5.1%)	0.007*	18 (2.8%)
Liver Failure	4 (1.0%)	0 (0.0%)	-	4 (0.6%)
COPD	5 (1.3%)	5 (2.0%)	0.522**	10 (1.5%)
Dementia	2 (0.5%)	5 (2.0%)	0.116**	7 (1.1%)

Tumour Classification (TNM)			0.00***	
T0	25 (6.3%)	39 (15.4%)	-	64 (9.8%)
T1	168 (42.2%)	88 (34.8%)	-	256 (39.3%)
T2	83 (20.9%)	49 (19.4%)	-	132 (20.3%)
T3	12 (3.0%)	18 (7.1%)	-	30 (4.6%)
T4	110 (27.6%)	59 (23.3%)	-	169 (26.0%)
Nodal Status (TNM)			0.879***	
N0	287 (72.1%)	182 (71.9%)	-	469 (72%)
N1	48 (12.1%)	34 (13.4%)	-	82 (12.6%)
N2	61 (15.3%)	35 (13.8%)	-	96 (14.7%)
N3	2 (0.5%)	2 (0.8%)	-	4 (0.6%)
Metastasis (TNM)			0.78***	
M1	4 (1.0%)	2 (0.8%)	-	6 (0.9%)
Surgical Procedure				
Mucosal Resection	339 (85.2%)	178 (70.4%)	0.000*	517 (79.4%)
Neck Dissection	244 (61.3%)	138 (54.55)	0.104*	382 (58.7%)
Complex Reconstruction	200 (50.3%)	92 (36.4%)	0.001*	292 (44.9%)
Median Post-Operative Length of Stay in Days (Range)	10 (0 - 71)	11 (0 - 65)	-	10 (0 - 71)
Inpatient Post-Operative Mortality	1 (0.3%)	8 (3.2%)	0.03**	9 (1.4%)
Post-Operative Inpatient Morbidity				
All Cause	116 (29.1%)	72 (28.5%)	0.92*	188 (28.9%)
Fistula	5 (1.5%)	6 (2.45%)	0.617*	12 (1.8%)
Infection	55 (13.8%)	47 (18.6%)	0.129*	102 (15.7%)
Pneumonia	11 (2.8%)	16 (6.3%)	0.043*	27 (4.1%)
Pressure injury	5 (1.3%)	6 (2.4%)	0.445*	11 (1.7%)
PE or DVT	10 (2.5%)	3 (1.2%)	0.389**	13 (2.0%)
AMI	2 (0.5%)	3 (1.2%)	0.382**	5 (0.8%)
Chyle Leak	2 (0.5%)	0 (0.0%)	-	2 (0.3%)
Delayed Cannulation	8 (2.0%)	0 (0.0%)	-	8 (1.2%)
Delayed Healing	3 (0.8%)	2 (0.8%)	0.644**	5 (0.8%)
Flap Complication	23 (5.8%)	7 (2.8%)	0.111*	30 (4.6%)
Haemorrhage	17 (4.3%)	2 (0.8%)	0.007**	19 (2.9%)
Necrosis	3 (0.8%)	0 (0.0%)	-	3 (0.5%)
Nerve Palsy	5 (1.3%)	0 (0.0%)	-	5 (0.8%)
Pneumothorax	3 (0.8%)	0 (0.0%)	-	3 (0.5%)
Return to theatre	26 (6.5%)	18 (7.1%)	0.898*	44 (6.85)

*Chi-squared with Yates continuity correction

***Pearson Chi-Squared

****Independent samples t-test (partial eta squared = 0 .023)

TABLE 2

Table 2. Logistic regression predicting likelihood of experiencing a post-operative complication

Complication	B	S.E	Wald	p	Odds Ratio	95% Confidence Interval for Odds Ratio	
						Lower	Upper

Age	-0.01	0.01	1.97	0.161	0.99	0.98	1.00
Sex	0.49	0.20	6.20	0.013*	1.64	1.11	2.41
Diabetes without Complications	-0.45	0.43	1.08	0.298	0.63	0.27	1.49
Diabetes with Complications	2.67	0.74	13.01	0.000**	14.43	3.39	61.49
Current Smoker	-0.09	0.23	0.15	0.695	0.91	0.58	1.44
Renal Failure	0.75	0.55	1.89	0.169	2.13	0.73	6.22
CCF	2.68	0.68	15.45	0.000**	14.52	3.82	55.17
Liver Failure	-3.39	1.55	4.79	0.029*	0.03	0.00	0.70
COPD	0.23	0.82	0.08	0.778	1.26	0.25	6.27
Dementia	0.00	0.89	0.00	1.000	1.00	0.17	5.72

* $P < 0.05$

** $P < 0.005$

B = B coefficient

S.E = standard error

Wald = Wald chi-square test

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