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Postoperative myocardial injury after major head and neck cancer surgery

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Abstract

Background—Head and neck cancer patients often have multiple risk factors for coronary artery disease. Yet, little is known about the incidence of postoperative myocardial injury after major head and neck cancer surgery and its clinical relevance. The aim of the study was to determine the risk of postoperative myocardial injury in patients undergoing major head and neck cancer surgery.

Methods—Retrospective cohort study of all patients who underwent major head and neck cancer surgery (n=378) at a single major academic center from April 2003 to July 2008. Peak postoperative troponin I (TnI) concentration was the primary outcome.

Results—Of 378 patients, who underwent major head and neck cancer surgery, 57 patients (15%) developed an elevated TnI; 90% of which occurred within the first 24 hours after surgery. Pre-existing renal insufficiency (unadjusted OR [OR]: 4.60, 95% CI 1.53–13.82), coronary artery disease (OR: 2.33, 95% CI 1.21–4.50), peripheral vascular disease (OR: 2.83, 95% CI 1.31–6.14), hypertension (OR: 2.22, 95% CI 1.20–4.12), and previous combined chemotherapy and radiation (OR: 2.68, 95% CI 1.04–6.91) were associated with elevated postoperative TnI. Patients with elevated TnI had a significantly longer length of stay in the hospital (8.5 vs. 10.1 days; p= 0.014) and ICU (3 vs. 4.5 days; p= 0.001) and an 8-fold increased risk of death at 60 days after surgery (adjusted OR: 8.01, 95% CI 2.03 – 31.56). At one year, patients with an abnormal postoperative TnI were twice as likely to die (OR 1.93; 95% CI 1.02 – 3.63).

Conclusions—Patients who undergo major head and neck cancer surgery are at significant risk for postoperative myocardial injury which is a strong predictor of 60-day mortality after surgery. Monitoring of myocardial injury during the first postoperative days as well as optimizing preventive cardiac care may be helpful to reduce postoperative mortality.

Keywords

Myocardial infarction; Outcomes; Troponin

Introduction

Worldwide more than half a million new cases of head and neck cancer are diagnosed each year(1). Head and neck cancer is commonly caused by long-term tobacco and alcohol abuse (2). Long-term smoking and tobacco abuse not only increase the risk for cancer, but also for coronary artery disease and myocardial infarction. Most patients present with advanced stage cancer, and many will undergo treatment with surgery either as the initial therapy or as salvage surgery after previously failed radiotherapy or chemo-radiotherapy.

Surgery for head and neck cancer is complex and extensive as it commonly involves the resection of the tumor and uni- or bilateral radical neck dissection, and often requires transfer of a tissue flap for reconstruction(1). Major head and neck cancer surgery frequently lasts more than 8 hours, involves large fluid shifts and blood loss, and causes significant postoperative inflammation and pain. All these factors are considered important risk factors for postoperative myocardial injury.

Postoperative myocardial injury is common and a major contributor to surgical morbidity and mortality: Up to 40% of all patients with coronary artery disease who undergo major noncardiac surgery develop postoperative (silent) myocardial ischemia and between 2–4% suffer from myocardial infarction or cardiac death (3–6). Postoperative myocardial infarction is associated with a 27–40% mortality rate at 30 days after surgery (7).

The cardiac risk after major vascular surgery has been studied extensively; yet, although head and neck cancer patients share many of the same risk factors for atherosclerotic disease, the cardiac risk after major head and neck cancer surgery has largely been overlooked (8–10).

Since 2003, Barnes-Jewish-Hospital has implemented standardized, serial troponin measurements after all major head and neck cancer surgeries. Troponin is a myocardial protein and biomarker, and as such the gold standard for diagnosing myocardial injury. As a consequence, we were able to study the incidence of postoperative myocardial injury in a large cohort of this patient population.

Methods

Study Design and Population

In this retrospective cohort study all consecutive patients were included who underwent major head and neck cancer surgery at Barnes-Jewish-Hospital, St. Louis, MO, between April 2003 and July 2008 and had a postoperative troponin I (TnI) test measured (n=378). Major head and neck cancer surgery was defined as surgical procedures that included at least the resection of a primary tumor and neck dissection. Patients were excluded if the sentinel surgery was for diagnostic purposes only or did not include resection of a major area of tissue within the head and neck region (n=278 out of 656). Consequently, these procedures were considered minor and patients did not have a postoperative TnI test drawn. Patients were also excluded if the diagnosis was not head and neck cancer (erroneous listing). TNM staging information was not available, but we used the SEER staging criteria instead which allow for a similar description of the disease extent.

Patients routinely had a preoperative cardiac evaluation performed by an anesthesiologist in the Preoperative Anesthesia Clinic. Only a minority of patients was seen additionally by a cardiologist and only per surgeon's or anesthesiologist's request. There were no formal criteria for involvement of cardiologists in the preoperative assessment. All patients were entered in a head and neck cancer database of the Washington University Department of

Otolaryngology. Individual patients' records were assessed from the Department of Otolaryngology medical records office or the Health Information Management Department at Barnes-Jewish Hospital either electronically or, in the case of older charts, by microfiche paper charts. Overall survival status was determined from a combination of the hospital-based tumor registry, the department-based head and neck cancer registry, or the Social Security Death Index (SSDI). The final survival status was determined as of Aug 24th 2009.

Comorbidity refers to the other diseases, illnesses, or conditions that a cancer patient has at the time of diagnosis and that may impact on treatment selection and outcome (11). For this project, the overall severity of comorbidity at diagnosis was classified as none, mild, moderate, or severe using the Adult Comorbidity Evaluation 27 (ACE-27) (12).

Assessment of postoperative myocardial injury

Myocardial injury was assessed by at least three serial troponin I (TnI) measurements: (1) immediately after surgery in the post-anesthesia care unit, (2) 8 hours after surgery and (3) 16 hours after surgery. Troponin I measurements could be cancelled or additional ones ordered at the discretion of the clinical care team. Commonly, additional TnI tests were ordered when an elevated TnI was detected to determine the peak TnI concentration.

Myocardial injury was defined as an elevated, abnormal TnI test at any postoperative timepoint. Cardiac troponin I measurements were made by the Dimension RxL method (Dade Behring, now Siemens Healthcare) which was modified in 2003 to eliminate interference from HAMA antibodies thereby improving low-end precision.(13) Initially, the clinical cut-off was a TnI concentration ≥ 0.1 ng/ml, but during the last 3 years of the study period the cut-off was lowered to 0.07 ng/ml due to the use of the more sensitive TnI assay. Myocardial infarction was defined according to the recently published universal definition of myocardial infarction(14): elevated TnI plus ECG changes consistent with myocardial ischemia and/or clinical symptoms of ischemia.

Statistical Analysis

Standard descriptive statistics were used to describe the distribution of main characteristics in patients with normal and elevated troponin levels. Mann-Whitney U and Chi-square tests were used to investigate the presence of relationship between abnormal troponin and continuous and categorical level characteristics, respectively. The odds ratios (OR) produced by univariate logistic regression were used to identify the strength of such relationships and the influence of abnormal troponin in short-term and long-term survival. Significant predictors, identified from univariate logistic regression, were included in a multivariate logistic regression model. Kaplan-Meier survival analysis as well as a Cox-proportional hazards model was used to compare the overall survival between patients with normal and abnormal troponin levels. The log-rank test was used to assess the statistical significance of the observed survival differences among groups. The statistical analysis was performed using the SPSS 17.0.2 software package (SPSS Inc., Chicago, IL). Two tailed tests of significance were used, and significance was established at the $p < 0.05$ level. This study was approved by the Washington University School of Medicine Human Studies Committee and granted a waiver of informed consent.

Results

A total of 378 patients who underwent major head and neck cancer surgery were included in the data analysis. The initial screen of the head and neck cancer patient database resulted in 656 patients of whom 278 had to be excluded. The majority of excluded patients (87%) did

not undergo major head and neck cancer surgery and consequently did not have a postoperative troponin test ordered.

Fifty-seven patients (15%) developed an elevated abnormal troponin I (TnI) test after surgery. Most patients with abnormal peak TnI levels ($n=43$, 75%) experienced a TnI elevation in the 0.07 – 0.2 ng/ml concentration range (Figure 1A). TnI levels peaked after a median of 10 hours after surgery (range 0 – 72 hours) and 90% of all peak TnI levels occurred within the first 24 hours after surgery (Figure 1B). Of the 57 patients with an abnormal TnI test, 19 (33%) underwent a cardiology consultation, 10 (18%; 2.6% of total population) had concurrent ECG changes consistent with an acute myocardial infarction and 2 (3.5%) underwent emergent cardiac catheterization and percutaneous transluminal coronary angioplasty (PTCA).

Predictors for elevated postoperative TnI

To identify predictors for elevated postoperative TnI, a univariate analysis was performed in which several variables were significantly associated with elevated postoperative TnI (Table 1). Pre-existing renal insufficiency was associated with a nearly 5-fold higher risk for elevated postoperative TnI. Coronary artery disease, peripheral vascular disease and hypertension increased the risk between 2.2- and 2.8-fold. Patients who underwent previous combined chemotherapy and radiation had a 2.7-fold increased risk, while chemotherapy or radiation therapy alone did not increase the risk. Similar odds ratios of 2 were observed in patients with congestive heart failure and of higher age (>74 years), although these were not statistically significant. Neither smoking history, intraoperative blood loss, intraoperative hypotension nor SEER tumor staging were significant predictors. However, the use of tissue flaps for reconstruction was associated with a 1.7-fold increased risk of postoperative myocardial injury (OR 1.71, 95% CI: 0.96 – 3.04, $p=0.07$), which was marginally non-significant. Patients with tissue flaps had a higher blood loss (771 ml vs. 442 ml, $p<0.0001$). The duration of surgery and time under general anesthesia was similar between patients with an elevated and patients with a normal postoperative TnI test.

In a multivariate logistic regression analysis, several predictors for postoperative TnI elevation identified earlier as significant predictors in the univariate analysis remained independently significant (Table 2). These predictors were: renal insufficiency, hypertension, and preceding combined chemotherapy and radiation. However, due to multicollinearity, several predictors (e.g.; peripheral vascular disease) had to be removed from the model to assure stability.

Elevated postoperative TnI and outcomes

In a next step, the relationship between elevated postoperative TnI and short- and long-term outcomes after head and neck cancer surgery was assessed. Patients with postoperative myocardial injury had a significantly longer length of stay in the hospital (median stay 8.5 vs. 10.1 days; $p=0.014$) and ICU (median stay: 3 vs. 4.5 days; $p=0.001$). Postoperative myocardial injury was associated with a 6-fold increased risk of death at 30 days after surgery and an 8-fold increased risk of death at 60 days after surgery (Table 3). Elevated TnI (adjusted OR 8.01; 95% CI 2.03 – 31.56, $p=0.003$) and chemotherapy (adjusted OR 10.36; 95% 0.90 – 118.89) were the strongest predictors of 60-day mortality in a multivariate regression model (Table 4). At one year, patients with an abnormal postoperative TnI were twice as likely to die (figure 2; OR 1.93; 95% CI 1.02 – 3.63; $p=0.04$). Long-term outcome over a 7-year period, using Kaplan-Meier survival analysis, was similar between patients with normal and elevated postoperative TnI. No difference in median survival was found between patients with an acute postoperative myocardial infarction versus TnI elevation (569 vs. 652 days, $p=0.90$).

Discussion

The results of this study show that a substantial number of patients who undergo major head and neck cancer surgery experience postoperative myocardial injury. Furthermore, patients who developed postoperative troponin elevation had longer lengths of stays in the ICU and hospital and were at considerably higher risk of death (6–8-fold) within the first 60 days after surgery. The increased mortality risk persisted for the whole first year after surgery.

The results of this study also show that the cardiac risk after major head and neck cancer surgery was considerably underestimated from several smaller retrospective studies where the incidence of myocardial infarction after major head and neck cancer surgery was reported between 0.2– 3.6% (8,10,15–19). All these studies relied on retrospective identification of myocardial infarction diagnosed by clinical signs and ECG. In the only study that included postoperative troponin tests, 16 out of 65 (25%) patients had signs of myocardial injury (9). It now seems likely that the incidence rate of postoperative myocardial injury after major head and neck cancer surgery approaches that after major vascular surgery. Large-scale studies in major vascular surgery observed postoperative myocardial injury rates between 14 – 38% (20–24). Head and neck cancer patients share a similar risk profile with patients suffering from peripheral vascular disease predisposing them to atherosclerotic disease in addition to head and neck cancer. As with major vascular surgery patients, an abnormal TnI test indicates a substantially increased short-term mortality risk. We observed an 8-fold increased risk for death at 60 days among head and neck cancer patients, which is similar to a 6-fold increased mortality rate at 6 months after major vascular surgery (25). Of particular clinical interest is the observation that even small troponin I elevations, in the range of 0.1 – 0.2 ng/ml (“troponin leaks”) where the majority of observed peak TnI values in our study was, are associated with important clinical events and outcomes. It is unlikely that small TnI elevations are directly causing adverse outcomes and increased mortality; rather they seem to indicate a very vulnerable patient population at high risk of subsequent myocardial infarction and death.

Our study corroborates the importance of well-known risk factors for postoperative myocardial injury, such as pre-existing coronary artery disease, peripheral vascular disease, renal insufficiency, and hypertension (3). Of note, however, is the fact that only 30% of patients, who developed a postoperative TnI elevation, had a preoperative diagnosis of coronary artery disease. This indicates that coronary artery disease is likely under-diagnosed among head and neck cancer patients and clinicians should be suspicious about the presence of coronary artery disease in these patients. Unique among our study population was the increased cardiac risk associated with the use of flap procedures for reconstruction and previous treatment with both chemotherapy and radiation. Flap reconstructions typically last longer and are associated with more fluid shift, a substantially larger surgical area, and subsequently more surgical stress. Although not measured in the current study, we believe these variables contribute to the higher incidence of postoperative myocardial injury.

Anticancer chemotherapy is known to be cardiotoxic (26) and it appears that chemotherapy increases the postoperative cardiac risk after head and neck cancer surgery. The most frequent cytotoxic agents used to treat head and neck cancers are cisplatin and 5-fluorouracil which have nephrotoxic and cardiotoxic effects, respectively (27,28). Additionally, combined use of chemotherapy and radiation is associated with higher treatment-related toxicities than use of radiation alone (29,30). Thus, patients undergoing salvage surgery after previous treatment with both chemotherapy and radiation may be less resilient to the additional stresses related to subsequent major surgery.

This study had several strengths and limitations. The strengths include the fact that we were able to study a large cohort of consecutive major head and neck cancer surgeries performed over 6 years at a single academic centre. Moreover, we were able to assess postoperative myocardial injury in a largely unbiased and complete fashion since serial troponin I testing was routinely done after all major head and neck cancer surgeries. The availability of and reliance on troponin I as the main outcome variable negated the need to use myocardial infarction diagnosed by clinical signs or ECG only as primary outcome.

Limitations include our inability to assess preoperative troponin I levels. Despite the theoretical possibility that some patients had abnormal TnI levels before surgery, several large scale studies, including our own current, show that this is uncommon.(31,32) Despite having enrolled a large cohort of head and neck cancer patients, several important pre-existing conditions that were previously linked with postoperative myocardial injury, such as congestive heart failure, were too infrequent in our sample to be adequately statistically tested. Furthermore, a clear limitation of the study is that we were unable to assess the causes of death by having to rely on the Social Security Death Index. While highly suggestive, the large increase in short-term mortality could not be unequivocally attributed to cardiovascular causes. Based on the pattern of the two survival curves, it seems likely that within the first year after surgery, and particularly within 60 days, cardiovascular causes play a dominant role whereas cancer-related deaths increase thereafter. Other causes of death, however, are also plausible.

The clinical implications of this study are severalfold. First, patients who undergo major head and neck cancer surgery should be considered a vulnerable patient population at high-risk for postoperative myocardial injury. Therefore, close cardiac monitoring for myocardial injury particularly within the first 24 hours after surgery, ideally by serial troponin measurements, seems prudent. Second, even small elevations of postoperative troponin should be considered a “red flag”, identifying a patient at significant risk of myocardial infarction and death within the first 60-days after surgery. Based on our data, we would recommend that most patients undergoing major head and neck cancer surgery should be followed with serial postoperative troponin tests, particularly patients with cardiac risk factors. Moreover, patients who develop an elevated troponin should be optimized regarding their cardiac care, for instance being started on aspirin, statins, or β -blockers in agreement with cardiology.

In conclusion, this study shows that patients who undergo major head and neck cancer surgery are at significant risk for postoperative myocardial injury. Patients who develop myocardial injury after head and neck cancer surgery have an 8-fold increased mortality rate within the first 60 days after surgery. Based on this evidence, patients should be closely monitored for myocardial injury after major head and neck cancer surgery, ideally with cardiac troponin measured during the first postoperative day. Primary and secondary prevention of myocardial infarction should be optimized for these patients.

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Figure 1. Distribution of individual observed peak troponin I levels and time interval when troponin I levels peaked after surgery

A Individual troponin I peak concentrations of all 57 patients with elevated postoperative troponin I elevation. **B** Histogram showing the time interval after surgery when postoperative peak troponin I elevation occurred. 90% occurred within the first 24 hours.

Figure 2. Kaplan-Meier Survival Analysis of Patients with normal and elevated Postoperative Troponin I

Patients with elevated postoperative troponin I have a 2-fold increased risk of death during the first year after surgery ($p=0.03$). Long-term survival at 6 years is not different between the groups.

Table 1

Characteristics of the Study Population and Univariate Comparison

	Troponin I Normal N=321 (85%)	Troponin I Abnormal N=57 (15%)	OR	95% CI	P-value
Age (years) Median (Min-Max)	62.6 (29–101)	66.8 (31–87)	1.02	1.00–1.04	0.116
Gender					
Male	235 (73)	44 (77)	1.0	--	
Female	86 (27)	13 (23)	0.81	0.42–1.57	0.528
Race					
White	293 (91)	52 (91)	1.0	--	
Black	25 (8)	5 (9)	1.13	0.41–3.08	0.816
Asian	2 (1)	0	0	0	0.999
BMI Median (Min-Max)	25.6 (12.5–63.3)	26.7 (18.0–48.7)	1.03	0.99–1.07	0.139
Smoking History					
Never	73 (23)	17 (30)	1.0	--	
< 20 pack-years	34 (11)	5 (8)	0.63	0.22–1.85	0.403
>=20 pack-years	201 (62)	34 (60)	0.73	0.38–1.38	0.328
Unknown pack-years	13 (4)	1 (2)	0.33	0.04–2.70	0.302
Coronary Artery Disease	46 (14)	16 (28)	2.33	1.21–4.50	0.011
Peripheral Vascular Disease	25 (8)	11 (19)	2.83	1.31–6.14	0.006
Congestive Heart Failure	17 (5)	6 (11)	2.10	0.79–5.59	0.128
Hypertension	172 (54)	41 (72)	2.22	1.20–4.12	0.011
Renal Insufficiency	8 (3)	6 (11)	4.60	1.53–13.82	0.003
Comorbidity Index					
None	30 (9)	3 (5)	1.0	--	
Mild	109 (34)	14 (25)	1.28	0.35–4.76	0.708
Moderate	95 (30)	23 (40)	2.42	0.68–8.63	0.173
Severe	87 (27)	17 (30)	1.95	0.54–7.14	0.311
SEER tumor staging					
In situ	1 (1)	2 (3)			
Local	115 (36)	20 (35)			

	Troponin I Normal N=321 (85%)	Troponin I Abnormal N=57 (15%)	OR	95% CI	P-value
Regional	197 (62)	34 (60)			
Distant	3 (1)	1 (2)			0.974
Prior cancer treatment					
No chemo or radiation	251 (78)	41 (73)	1.0	--	
Chemo only	5 (2)	1 (1)	1.22	0.14–10.75	0.902
Radiation only	49 (15)	7 (13)	0.89	0.38–2.11	0.625
Chemo-Radiation	16 (5)	7 (13)	2.68	1.04–6.91	0.031
Intraoperative Hypotension	162 (51)	29 (53)	1.05	0.59–1.87	0.859
Amount of blood loss (ml)	400 (2–3500)	450 (10–2400)	1.0	1.0–1.0	0.491
Length of surgery (hrs)	8.0 (0.8 – 20.8)	8.8 (1.5 – 20.7)	1.01	0.95 – 1.09	0.730
Use of flaps for reconstruction					
No flap	225 (70)	33 (58)	1.0	--	
Flap	96 (30)	24 (42)	1.71	0.96 – 3.04	0.07

Table 2

Results of the Multivariate Analysis identifying Predictors for Elevated Postoperative Troponin I

Variables	adjusted OR	95% CI	P
Renal Insufficiency	4.08	1.32– 12.66	0.015
Hypertension	2.35	1.23 – 4.48	0.009
Chemo-Radiation	3.05	1.15 – 8.10	0.025
Coronary Artery Disease	1.84	0.92 – 3.71	0.086
Use of flaps for reconstruction	1.72	0.93 – 3.21	0.087

Table 3
The Relationship Between Troponin Status and Various Mortality Time Outcomes

Mortality	Troponin I Normal N=321 (85%)	Troponin I Abnormal N=57 (15%)	OR	95% CI	P-value
30 days	2 (0.6%)	2 (3.5%)	5.80	0.80 – 42.04	0.08
60 days	4 (1.2%)	5 (8.8%)	7.62	1.98 – 29.31	0.003
1 year	58 (18.1%)	17 (29.8%)	1.93	1.02 – 3.63	0.043
2 years	103 (36.7%)	24 (43.6%)	1.34	0.75 – 2.40	0.330

Table 4

Predictors of 60-day survival.

Univariate analysis			
Variable	Unadjusted OR	95% CI	p-value
Elevated TnI	7.61	1.98–29.31	0.003
Chemotherapy	14.4	1.36–152.96	0.027
Chemo-Radiation	6.86	1.19–39.63	0.031
IDDM	5.57	1.08–28.76	0.04
Diabetes	4.29	1.12–16.45	0.034
Female gender	3.66	0.96–13.90	0.057
Multivariate Analysis			
Variable	Adjusted OR	95% CI	p-value
Elevated TnI	8.01	2.03 – 31.56	0.003
Chemotherapy	10.36	0.90 – 118.89	0.06