Do traditional risk stratification models for cerebrovascular events apply in irradiated head and neck cancer patients?

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Running title: Risk stratification and carotid artery stenosis in irradiated carotid arteries

ABSTRACT

Background

Primary radical radiotherapy (RT) for head and neck cancer (HNC) often results in significant radiation dose to the carotid arteries.

Aim

We assessed whether HNC patients are at increased risk of a cerebrovascular event primarily due to RT or other risk factors for atherosclerosis by: (i) risk-stratifying patients according to validated QRISK-2 and QSTROKE scores, (ii) comparing the prevalence of carotid artery stenosis (CAS) in irradiated and unirradiated carotid arteries.

Design

HNC patients treated with a radiotherapy dose greater than 50 Gy to one side of the neck $\geq$2 years previously were included.

Methods

QRISK-2 (2014) and Q-STROKE (2014) scores were calculated. We compared the prevalence of CAS in segments of the common carotid artery (CCA) on the irradiated and unirradiated sides of the neck.

Results

50 patients (median age of 58 yrs (interquartile range (IQR) 50 – 62)) were included. The median QRISK-2 score was 10% (IQR 4.4-15%) and the median QSTROKE score was 3.4% (IQR 1.4-5.3%). For both scores, no patient was classified as high-risk. Thirty-eight patients (76%) had CAS in one or both arteries. There was a significant difference in the number of irradiated arteries with stenosis (N=37) compared to unirradiated arteries (N=16)

(p<0.0001). There were more plaques on the irradiated artery compared to the unirradiated side (64/87) (73.6%) versus 23/87 (26.4%), respectively) (p<0.001).

Conclusions

Traditional vascular risk factors do not play a role in radiation-induced carotid atherosclerosis. Clinicians should be aware that traditional risk prediction models may under-estimate stroke risk in these patients.

BACKGROUND

Primary radical radiotherapy (RT) for head and neck cancer often results in significant incidental doses of radiation to the carotid arteries. For patients requiring lymph node irradiation, the treatment fields will extend from the mastoid process superiorly down to just below the clavicles inferiorly. Therefore, in this scenario, the common, internal, and external carotid arteries (and some of their branches) will receive full radiation dose as lymph nodes are located in close proximity to the vessels (Figure 1). Carotid artery stenosis (CAS) is a risk factor for subsequent neurological sequelae. [1-3] Radiotherapy to the cervical vessels is associated with increased CAS [4-6] and increased incidence of stroke. [7]

Several factors are associated with increased stroke risk: increasing age, smoking, diabetes mellitus, hypertension, hypercholesterolaemia, obesity and radiotherapy (RT) to the affected vessels.[8] Patients with head and neck cancer may have one or more risk factors associated with stroke risk, as smoking and increased alcohol consumption are risk factors for the development of head and neck cancer [9 10] and head and neck cancer is more common in patients over 60 years of age.

Quantifying stroke risk in patients is assisted by the use of several validated scores that are calculated based on risk factors. There are several risk prediction models available but, more recently, the Q-RISK2 and QSTROKE scores have been developed specifically to determine cardiovascular risk in UK populations. [11 12] The QSTROKE score was specifically designed to aid general practitioners in predicting a patient's risk of developing a stroke. A 10-year risk of cardiovascular disease of 20% or greater is considered high risk, 10% to <20% is intermediate risk, and <10% low risk.[13] Long-term survivors of head and neck cancer are often discharged to their primary care physicians after 5 years of follow-up, yet these patients may develop significant CAS and experience a neurological event after this

follow-up period. General practitioners may use these recommended risk prediction models to risk-stratify these patients for future cardio- and cerebrovascular risk.

Therefore, in order to assess whether patients with head and neck cancer treated with cervical RT are at increased risk of a cerebrovascular event primarily due to the radiotherapy or because these patients have other risk factors for atherosclerosis, this study was designed to (i) risk-stratify patients according to validated QRISK-2 and QSTROKE scores based on traditional risk factors for atherosclerosis, and (ii) compare the prevalence of CAS in irradiated and unirradiated carotid arteries.

METHODS

Head and neck cancer patients treated with radical RT to just one side of the neck prior to December 2009 were included. Ethical approval was obtained from a regional Research Ethics Committee and the protocol for the study were reviewed by the Royal Marsden Committee for Clinical Research (CCR3687) and registered on clinicaltrials.gov (NCT02060643).

Written informed consent was obtained from each participant and medication history and co-morbidities were recorded. Blood pressure, height and weight (to determine body mass index) were measured and electrocardiogram (ECG) was performed. Blood samples were taken for haemoglobin, plasma glucose, lipid profile, renal and liver profile.

QRISK-2 and QSTROKE

The QRISK-2 (2014) and Q-STROKE (2014) scores were calculated using online calculators (www.qrisk.org and www.qstroke.org, respectively) to determine each patient's 10-year risk of cardiovascular and cerebrovascular disease, respectively. Details of each patient's age, sex, race, co-morbidities, medication, systolic blood pressure, body mass index and

cholesterol to high-density lipoprotein (HDL) ratio were inputted into each calculator to determine a percentage 10-year risk.

Ultrasound studies

Carotid ultrasonography was performed for all participants using a high-resolution B-mode ultrasound system (Vivid-7; General Electric Healthcare, Chalfont, Bucks, UK) equipped with a broadband linear array (3-11 MHz) transducer. All scans were performed by cardiologists who were blinded to the patient's prior history including the laterality of RT. ECG monitoring was performed continuously throughout the scan and arterial blood pressure was recorded using an automated sphygmomanometer.

Segments of the CCA – proximal, mid, distal, and bifurcation, and the proximal portion of the internal carotid (ICA) and external carotid arteries (ECA) on both sides of the neck were examined with the patient supine on an examination couch. The carotid waveforms, peak systolic (PSV) and end-diastolic velocities (EDV) were assessed online and recorded for the internal carotid artery and spectral measurements taken with a Doppler angle of 55 to 65 degrees. Four-beat video loops (long-axis and short-axis) of each segment of the CCA and the internal and external branches were stored for offline analysis.

ICA stenosis

The diagnostic criteria for ICA stenosis were based on PSV and EDV as well as ICA/CCA ratios. Standard criteria for measuring ICA stenosis were used,[14] and assessments were performed offline.

The degree of stenosis is classified as follows: Mild stenosis: 0 to 29%; Moderate stenosis: 30% to 69%; Severe stenosis: 70% to 99%; Total occlusion: >99%.

Plaque definition and non-ICA stenosis

Plaque was defined using the Mannheim consensus: a focal structure encroaching into the arterial lumen by >0.5 mm, a distinct area of IMT >50% greater than the adjacent wall or >1.5 mm in thickness.[15] The percentage stenosis was calculated offline using the NASCET method, and is defined as the diameter of the normal lumen distal (A) to the stenosis minus the residual lumen at the site of stenosis (B) divided by A multiplied by 100 (Figure 2).[16] For non-ICA plaques, the percentage stenosis was calculated only. The number and location of plaques on each side of the neck was recorded. For arteries with multiple discrete plaques, each plaque was graded separately.

We looked at the effect of surgery on the prevalence of CAS by considering the unirradiated side of the neck and comparing the number of plaques in those treated with neck dissection to those that did not have a neck dissection. A previous study reported that more patients had stenosis if they had had a neck dissection compared to those treated with RT alone.[17] This was an unexpected finding, as increased prevalence of carotid artery stenosis following surgery alone has not been observed.[18]

Statistical Considerations

Sample size

Sample size calculation was based on the results from a previously published retrospective study by Dorresteijn et al,[19] which looked at the difference in carotid intima medial thickness between irradiated (mean 1.13 mm) and unirradiated (mean 0.83 mm) carotid arteries. With a significance level (α) of 0.05 and 80% power, the sample size required was 45 (using a paired t test with mean difference of 0.3 and standard deviation (SD) of 0.7). Therefore, 50 patients were recruited over an 18 month period to account for poor ultrasound windows that may limit image acquisition in a proportion of patients. Although the calculation of the sample size for this current study was based on a different endpoint (CIMT), a study by Brown et al calculated a sample size of 40 patients would be required to show a difference in

stenosis using internal matched controls.[17] Therefore, it is unlikely that our study is underpowered to show a difference.

Statistical analysis

Patient characteristics were summarised using descriptive statistics. Quantitative variables were expressed as means (+/- standard deviations) and medians (including ranges) and qualitative variables were expressed as frequencies and percentages. The use of risk-modifying therapy was summarised in tabular form as whole numbers of each type of therapy and percentage of total patients in that group. The prevalence of carotid stenosis in both irradiated and unirradiated carotid arteries was summarised as a percentage. Degree of carotid stenosis on both sides of the neck was displayed in tabular form. Differences in prevalence and degree of stenosis between the two sides of the neck were compared using the Chi-squared test. The effect of surgery on the prevalence of carotid artery stenosis and the total number of plaques on the irradiated side was calculated using the chi-squared test and Mann Whitney test, respectively. The prevalence of plaques in patient treated >5 years previously versus those treated <5 years previously was compared using the Mann Whitney test.

All statistical tests were considered two-tailed with significant difference at the $p<0.05$ level. Statistical analyses were undertaken using Stats Direct Medical Statistics and Graphpad Prism 6 statistical packages.

RESULTS

Patient demographics

Between January 2012 and June 2013, 50 patients were recruited in the study. One patient declined blood tests due to poor venous access. Demographic characteristics and risk

factors for atherosclerosis are summarised in table 1. Thirty-four patients (68%) had at least one risk factor for atherosclerosis. More than half of the patients (58%) received 60 Gy to the neck and 68% of patients were treated with neck dissection as well as radiotherapy. Almost half of patients (46%) received platinum-based induction and/or concomitant chemotherapy.

Radiation dose to carotid artery

Fourteen patients (28%) had radiotherapy to the hemi-neck with a uniform dose prescribed to the hemi-neck. The remaining 36 patients (72%) were treated with a wedged-pair (anterior and posterior radiotherapy beams to treat the ipsilateral hemi-oropharynx or parotid bed) and matched hemi-neck field (anterior and posterior radiotherapy beams to cover the ipsilateral lower neck nodes below the hyoid bone cranially down to the clavicle caudally) (see figure 1). The mean (standard deviation (SD)) maximum dose to the irradiated artery was 53 (13) Gy and 1.9 (3.7) Gy to the unirradiated side.

QRISK-2 and QSTROKE scores

The median QRISK-2 score was 10% (IQR 4.4-15%) and the median QSTROKE score was 3.4% (IQR 1.4-5.3%). QRISK-2 and QTROKE risk stratification are displayed in Figures 3 and 4. For the QRISK-2 score, the majority of patients are classified as low- or intermediate, with fewer than 5% in the high-risk category. For the QSTROKE score, no patient was classified as high-risk and fewer than 5% were classified as intermediate-risk.

Carotid artery stenosis

Of the 50 patients who underwent carotid ultrasonography, 38 patients (76%) had CAS in one or both arteries. Thirty-seven patients (74%) had carotid artery stenosis in the irradiated

artery and only one patient had plaque on the unirradiated side alone. There was a significant difference in the number of irradiated arteries with stenosis (N=37) compared to the number of unirradiated arteries with stenosis (N=16) (p<0.0001). Two patients with severe stenosis had extensive plaque throughout the CCA and were subsequently referred for vascular assessment.

In total, 87 plaques were identified. There was a significantly greater number of plaques on the irradiated artery compared to the unirradiated side (64/87) (73.6%) versus 23/87 (26.4%), respectively) (p<0.001). The majority of documented stenoses were located in the carotid bulb (40/87 = 46%) and internal carotid artery (14/87 = 16.1%), with the rest located in the proximal, mid or distal CCA or ECA. Table 2 demonstrates the number and degree of stenoses in the irradiated and unirradiated artery. On the irradiated side, there was no difference in the prevalence of plaque (presence of plaque = yes or no) in those treated more than 5 years previously (17/24 patients = 70.8%) compared to those treated fewer than 5 years previously (19/26 patients = 73.1%) (p>0.99).

Effect of surgery on carotid artery stenosis

On the irradiated side, there was no difference in the degree of stenosis in those patients who were treated with a neck dissection and radiotherapy compared to those who did not have a neck dissection (p=0.46) (Figure 5). There was also no significant difference in the total number of plaques in those treated with both surgery and radiotherapy compared to those who did not have surgery (P=0.70).

DISCUSSION

This study demonstrated greater prevalence of CAS in irradiated carotid arteries in a cohort of patients with low- or intermediate-risk scores for cardiovascular and cerebrovascular

disease based on traditional risk factors for atherosclerosis. No patient had cardiac RT because all of the tumours were located in the head and neck region above the clavicles. Cardiovascular risk was quantified to demonstrate risk prediction from traditional risk factors for atherosclerosis as 68% of patients had at least one risk factor. It is still unclear how traditional vascular risk factors for atherosclerosis affect this process after RT. Our study demonstrated no effect of surgery on ipsilateral CAS; a finding which has been previously reported.[18] It has been suggested that radiation-induced damage is less likely to be affected by these factors.[4] The degree of plaque on both sides of the neck seems out of proportion with the risk prediction for the cohort. The QSTROKE score did not categorize any patient as being high-risk and only 2.5% as intermediate-risk. This suggests that established atherosclerosis (CAS) due to RT is independent of traditional risk factors and does not fit into a standard risk prediction model. It is also clear that these risk prediction models cannot be applied in this setting and clinicians should be aware of the increased risk following RT, particularly after patients have been discharged from specialist follow-up (usually after 5 years) to the primary care setting. Indeed, some researches have suggested regular screening for CAS in long-term survivors following RT to the neck.[17 20]

We have demonstrated that most plaques in irradiated arteries develop in the bulb. Seventy-two percent of patients were treated with a wedged-pair and matched hemi-neck technique, with the match-line just cranial to the carotid bulb. As the wedged-pair fields would have been prescribed to a higher dose (65 or 60 Gy) than the hemi-neck fields (60 or 50 Gy), there may have been resultant hotspots at the level of the bulb and consequent higher RT doses in this region. This may be further investigated with modern dosimetric techniques in a prospective setting. This study also demonstrated that surgery does not appear to have an effect on the prevalence of CAS and suggests that combined modality treatment does not have an additive effect on vascular tissue compared to surgery or RT alone.

It is unclear why there were a considerable number of plaques on the unirradiated artery. Forty-six percent of patients were treated with chemotherapy in addition to radiotherapy. Vascular damage following platinum-based chemotherapy has been reported in patients treated with chemotherapy for testicular cancers,[21] a cancer primarily of young, healthy males with no atherosclerotic risk factors and often cured by chemotherapy alone i.e. without the possible confounders of surgery or RT. This may explain the considerable number of plaques on the unirradiated artery. It is important to remember, however, that chemotherapy effects would be expected to be equal on both sides of the neck and, therefore, would not explain the difference in the number and grading of plaques between the two sides of the neck. It is also possible that radiotherapy-induced damage to endothelial cells, with subsequent release of certain growth factors such as platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), as well as cytokines,[22] may have a systemic effect on vessels remote to the site of injury, but this requires further investigation.

The long latent interval from RT to the development of established atherosclerosis and neurological sequelae hampers investigation of this process and, importantly, the conduct of interventional clinical studies. Therefore, as in spontaneous atherosclerosis, early relevant biomarkers of radiation-induced atherosclerosis are required. There has been a lot of interest in recent decades in arterial wall thickening (carotid intima medial thickness (CIMT), a validated surrogate biomarker for cardiovascular and cerebrovascular events in spontaneous atherosclerosis) as an imaging biomarker of radiation-induced atherosclerosis. [7] Current evidence suggests increased CIMT may be detected as early as 6-12 months after RT, [23 24] making this an attractive surrogate biomarker for prediction of stroke risk.

We have shown no difference in the prevalence of plaques or the total number of plaques on the irradiated side in those patients treated more than 5 years previously compared to those treated fewer than 5 years previously. This is in contrast to previously reported studies which showed an increased prevalence after 15 years [17] and after 5 years.[20] Both studies had a longer median interval from RT of 90 months and 72 months, respectively, compared

to 53 months in our current study. It is, therefore, possible that, with longer follow-up, a significant difference in carotid stenosis prevalence may be seen. Our study does suggest, however, that an interval from RT of less than 5 years is unlikely to result in a significant increase in the prevalence of stenosis. Therefore, surrogate biomarkers for radiation-induced atherosclerosis should consider the likely time interval from RT to development of neurological sequelae in the development of risk prediction models in this setting, with one study reporting a median interval to cerebrovascular events of 10.2 years. [25]

CONCLUSION

This study demonstrated a significantly higher prevalence of CAS in irradiated arteries, in a cohort that would be considered low- or intermediate-risk based on a traditional risk prediction model. This supports the suggestion that traditional vascular risk factors do not play a role in radiation-induced carotid atherosclerosis. Clinicians should be aware that traditional risk prediction models for stroke may under-estimate the risk in these patients.

Conflict of Interest Notification

We declare no conflicts of interest

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Table 1. Patient demographics and risk factors for carotid atherosclerosis

Demographic characteristics/risk factors		Number (%) (N=50)
Female		16 (32%)
Age, median (interquartile range (IQR))		58 (50 – 62)
Histology	Squamous	39 (78%)
	Non-squamous	11 (22%)
Primary site	Tonsil	41 (82%)
	Parotid	9 (18%)
Tumour Stage	0	7 (14%)
	1	22 (44%)
	2	17 (34%)
	3	1 (2%)
	4	3 (6%)
Nodal Status	0	12 (24%)
	1	10 (20%)
	2	28 (56%)
Neck Dissection		33 (66%)
Induction Chemotherapy		7 (14%)
Concomitant Chemotherapy		23 (46%)
RT dose to neck (Gy)	50 Gy	20 (40%)
	60 Gy	29 (58%)
	63 Gy	1 (2%)
Interval since RT (months), median (IQR)		53.9 (42.3- 90.5)
Risk Factors	Diabetes	4 (8%)
	Hypertension	14 (28%)
	Dyslipidaemia	11 (22%)
	Smoker/Ex-Smoker	27 (54%)
Body Mass Index (kg/m^2), median (IQR)		26.5 (23.2 – 28.4)
Medication	Aspirin	13 (26%)
	ACE Inhibitors	5 (10%)
	5-HMG Co-A reductase Inhibitor	13 (26%)
Total Cholesterol , median (IQR)		5.1 (4.6 - 5.8)
Low Density Lipoproteins, median (IQR)		3.3 (2.6 - 3.7)
High Density Lipoproteins, median (IQR)		1.4 (1.2 – 1.7)

Table 2. Grading of stenosis in irradiated and unirradiated arteries (on the irradiated side, 37 patients had a total of 64 plaques, and 16 unirradiated arteries had a total of 23 plaques) (p<0.001)

CAS (N=87 plaques)	Irradiated carotid artery Number (%)	Unirradiated carotid artery Number (%)
Mild	40 (46)	15(17.2)
Moderate	21 (24.1)	8 (9.2)
Severe	3 (3.5)	0
Total occlusion	0	0
Total	64 (73.6)	23 (26.4)

Figure legends

Figure 1. Typical radiation treatment plan for a left tonsil cancer, showing dose colourwash (colours joining regions of the same dose) to the primary tumour treated with a wedged pair technique (A) and a matched lower neck field (B) to cover ipsilateral neck lymph node groups. The ipsilateral (left) common carotid artery (and some of its branches) is included in the radiation fields.
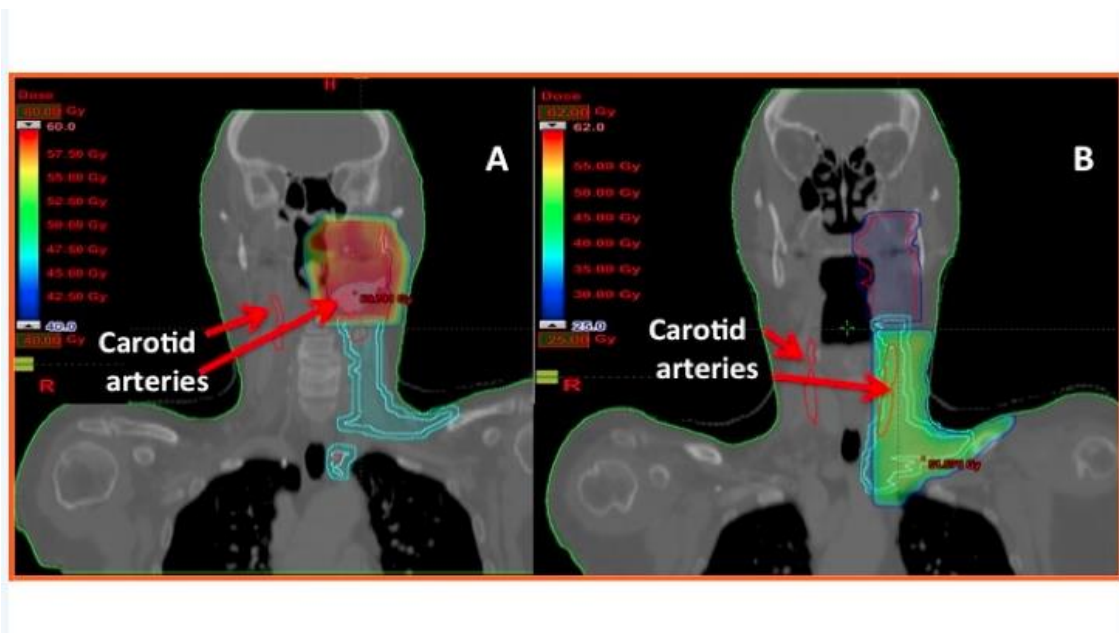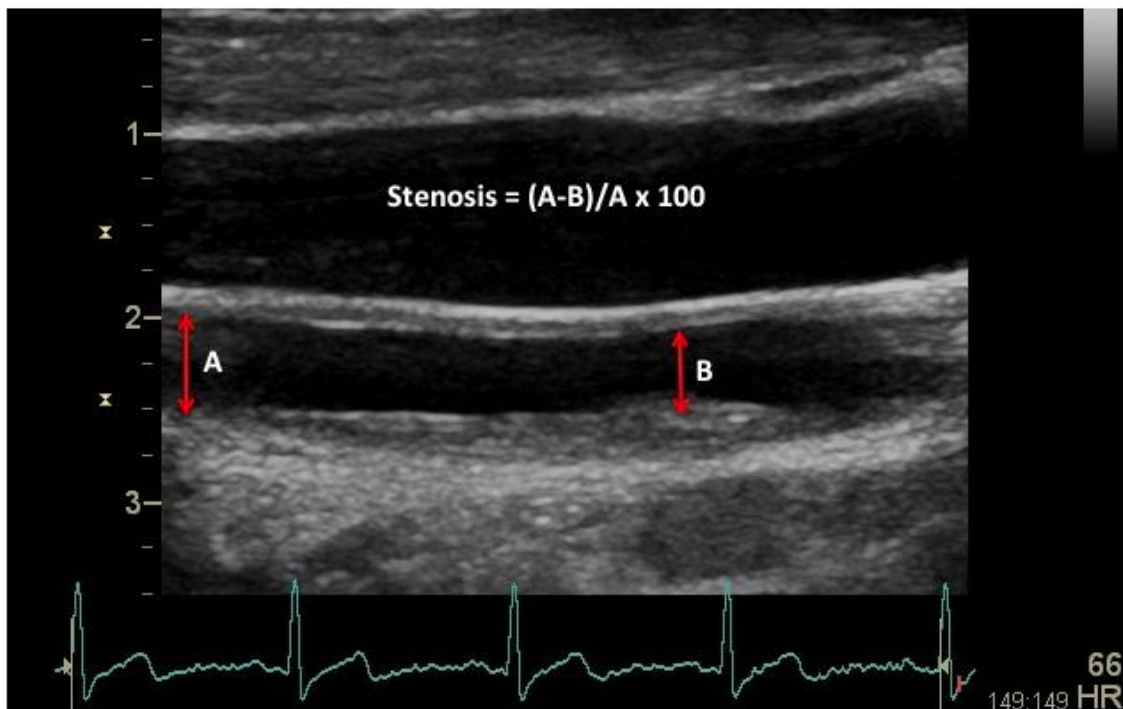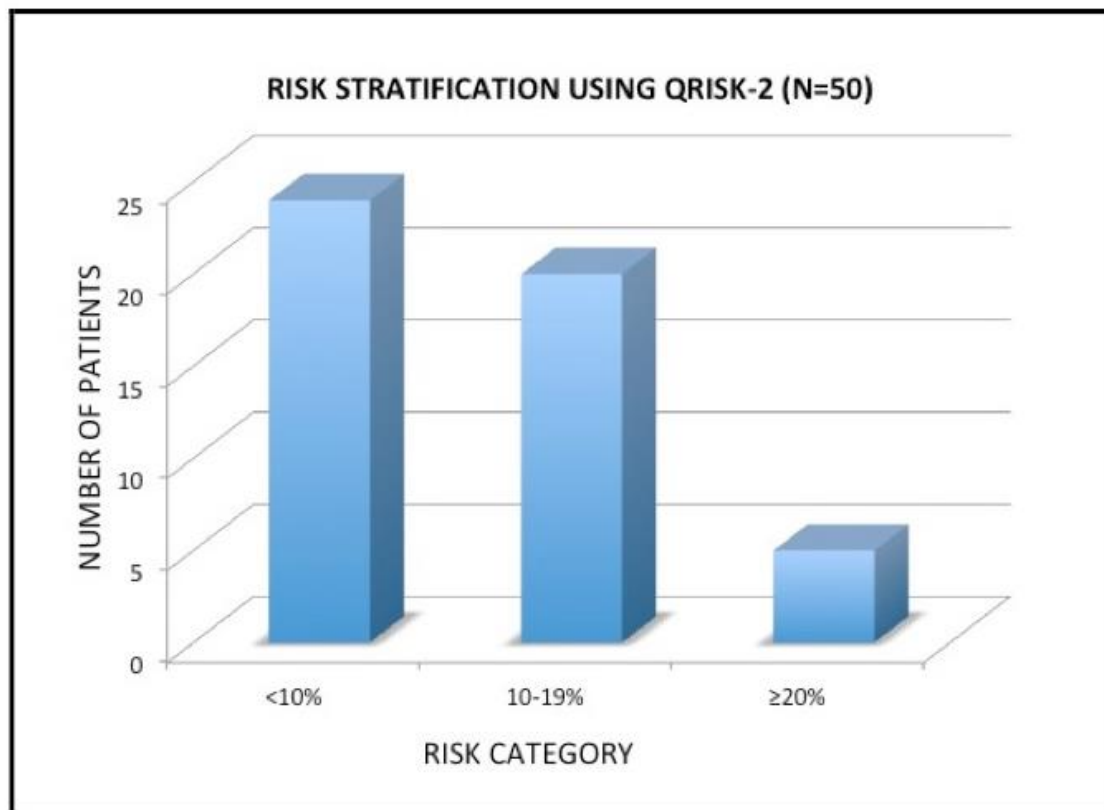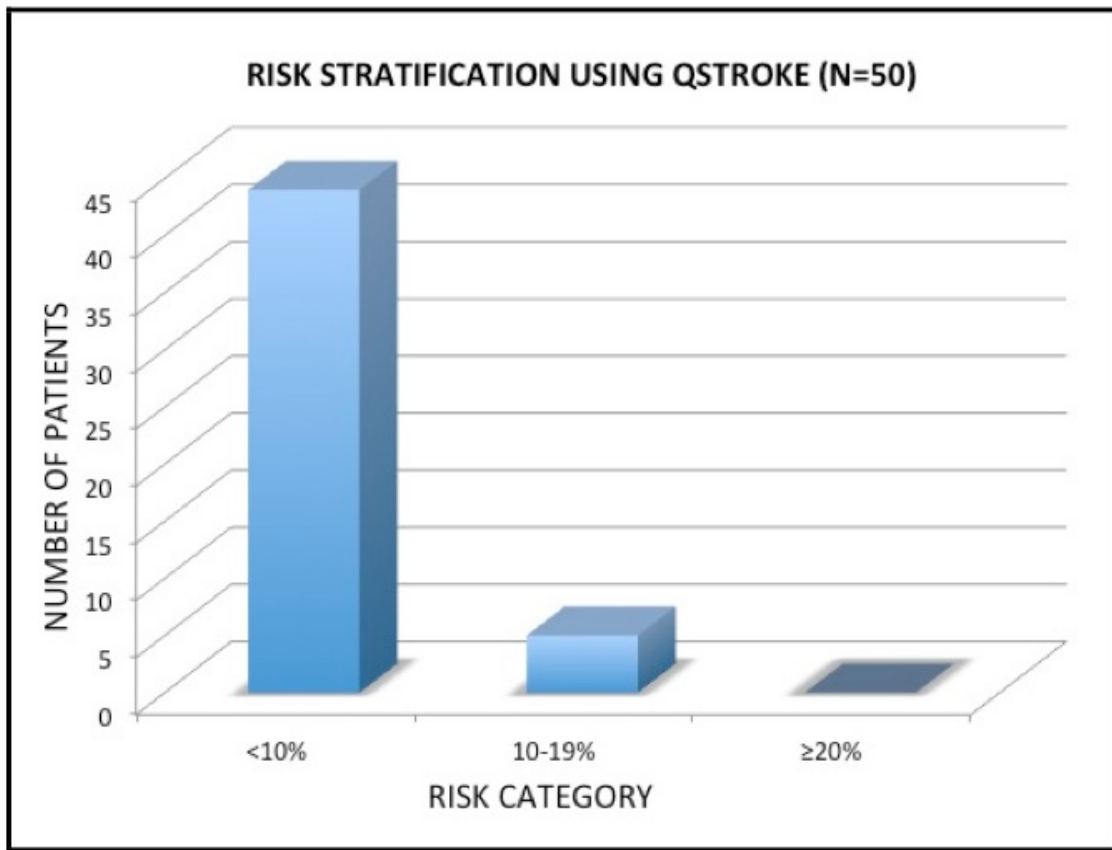
Figure 2. Calculation of percentage carotid artery stenosis in a patient with plaque using the NASCET method

Figure 3. Risk stratification using QRISK-2 score

Figure 4. Risk stratification using QSTROKE score

Figure 5. Number and degree of plaques on the irradiated side in patients who had surgery versus those who did not have surgery (p=0.70)