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FULL PAPER

Carotid dosimetry for T1 glottic cancer radiotherapy

K GARCEZ, MRCP, FRCR, **C C LIM**, MRCP, FRCR, **P WHITEHURST**, BSc, MSc, **D THOMSON**, MA, FRCR, **K F HO**, MD, FRCR, **M LOWE**, BSc, MSc, **A SYKES**, MRCP, FRCR, **LW LEE**, MRCP, FRCR, **B YAP**, FRCP, FRCR and **N SLEVIN**, FRCP, FRCR

Department of Clinical Oncology, Christie Hospital, Manchester, UK

Address correspondence to: Dr Kate Garcez
E-mail: *kate.garcez@christie.nhs.uk*

Objective: Radiotherapy for T1 glottic cancer is commonly delivered using a lateral parallel opposed pair of megavoltage photon fields. There is increasing reported evidence of cerebrovascular events due to radiation-induced carotid stenosis. An alternative field arrangement is to use an anterior oblique technique. This study compares the carotid dosimetry between the two techniques and reviews the evidence for the risk of radiation-induced vascular events.
Methods: The radiotherapy plans of 10 patients with T1 glottic cancer treated with an anterior oblique technique were examined for carotid dose. Alternative plans were then created using a parallel opposed pair of fields and the dose to the carotids compared. All patients received 50 Gy in 16 fractions treating once daily, for 5 days in a week.
Results: The average of the mean dose to the carotids with the anterior oblique technique was 21 Gy compared with 37 Gy using the lateral parallel opposed pair arrangement ($p < 0.0001$).
Conclusion: An anterior oblique field arrangement for the treatment of T1 glottic cancer results in a significantly lower radiation dose to the carotid arteries, which may be clinically important in terms of reducing the risk of cerebrovascular events in long-term survivors.
Advances in knowledge: Although the anterior oblique technique for treating early glottic cancers is well described, and it is predictable that the dose received by the carotid arteries should be lower with this technique, to our knowledge this is the first study to quantify that reduction in dose with a series of patients.

For other than clearly defined vocal cord lesions clear of the anterior commissure, radiotherapy remains the mainstay of curative treatment for T1 glottic cancer.[1,2] The radiotherapy target volume should be confined to the larynx without any attempt to encompass neck nodes. There is increasing reported evidence of late cerebrovascular events such as transient ischaemic attacks and ischaemic strokes due to radiation-induced injury of the carotid artery, *e.g.* accelerated arteriosclerosis. These vascular events can occur many years after radiotherapy such that their relationship to previous radiotherapy is obscured.

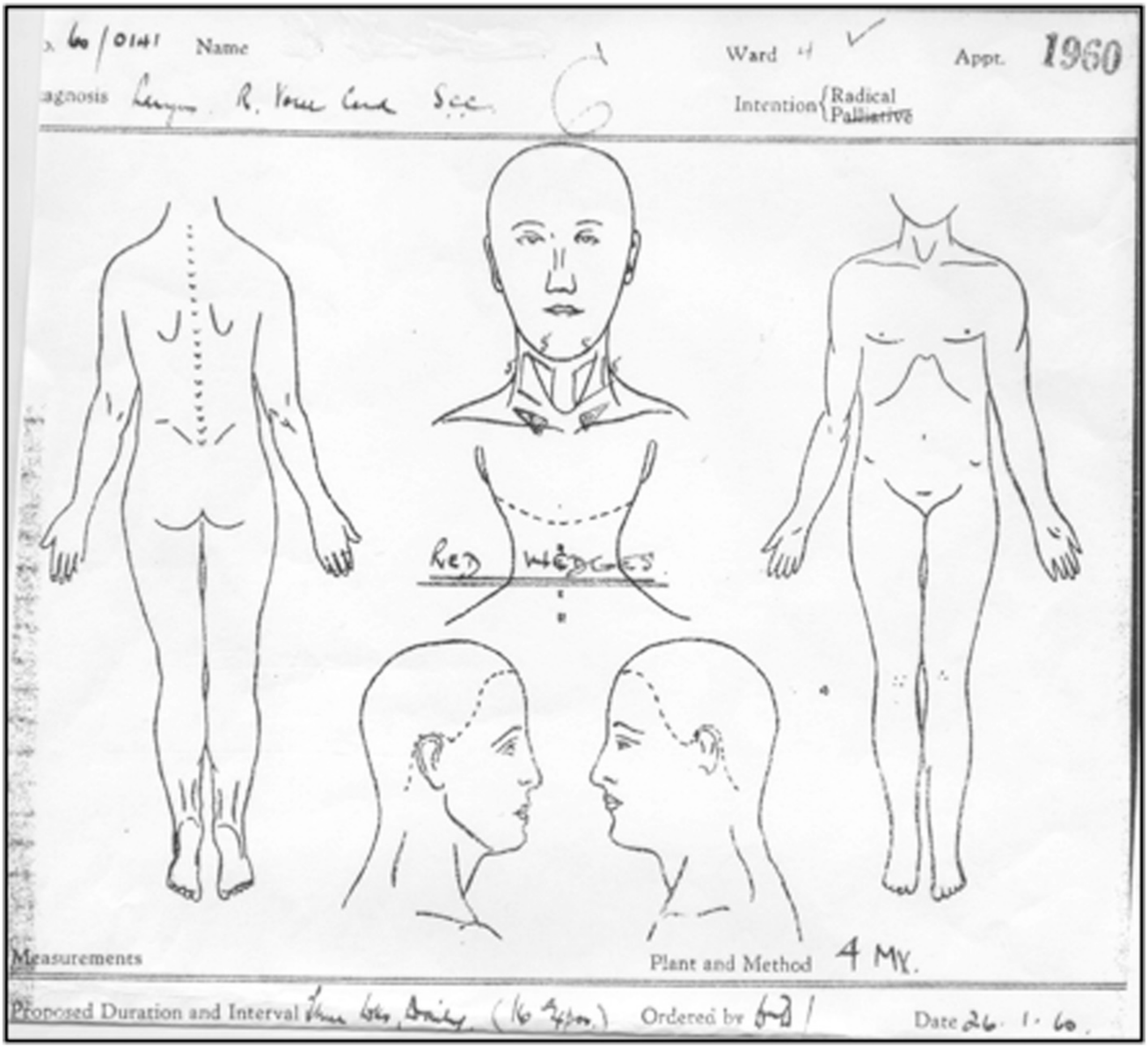
Classically, a lateral parallel opposed pair of megavoltage photon fields is used for the treatment of early glottic cancer. An alternative approach is an anterior oblique technique, which we adopted following the introduction of a linear accelerator in our centre in 1955 (Figure 1). We aim to assess the extent of carotid exposure, to compare the carotid dosimetry between anterior oblique and lateral parallel opposed pair techniques and also to review the evidence for the increased risk of vascular events.

METHODS AND MATERIALS

10 three-dimensional (3D) conformal, forward planned, radiotherapy plans for the radical treatment of T1 glottic cancer using an anterior oblique field arrangement were randomly selected. Our standard procedure for delineating the target volume (the larynx) was followed, using a CT planning scan with the patient positioned supine in an immobilization shell. The centre of the glottic larynx is then identified on the scan, and two anterior oblique wedged fields measuring 5.5 × 5.5 cm are applied, with a 2-mm bolus over the anterior commissure. The wedge angles are optimized to provide coverage of the target site by 95% of the prescription dose. A separate plan using a lateral parallel opposed wedged pair of fields was then generated for the same 10 cases using the same field sizes. The bilateral carotid arteries were outlined over a length of 8 cm. The spinal cord was also outlined as an organ at risk. The doses received by these structures using the two different techniques were compared. The planning system used was the Pinnacle3 v. 9.0 (Philips Medical Systems, Cleveland, OH).

The dose of radiotherapy for each case was 50 Gy in 16 fractions, treating once daily, for 5 days a week, using

Figure 1. Diagram showing the anterior oblique field arrangement.



4-MV photons, prescribed to the International Commission on Radiation Units and Measurements reference point.

Statistical analysis was carried out using a paired *t*-test to compare the mean difference in dose received by each carotid with the two different techniques. SPSS® v. 16 (SPSS Inc., Chicago, IL) was used.

RESULTS

The dose received by the carotid arteries with each beam arrangement is shown in Table 1. Both the maximum and mean doses were significantly lower with the anterior oblique technique.

The dose to the spinal cord was higher with the anterior oblique arrangement but still comfortably within tolerance. Figure 2 shows the dose–volume histogram for the two beam arrangements. An example of the two beam arrangements and position of the carotid arteries is shown in Figure 3.

DISCUSSION

Early glottic cancer treated with radical radiotherapy has an excellent outcome, with 5-year local control rates of 85–95%, cause-specific survival close to 100% and overall survival of approximately 85% at 5 years.[1,2] Because of long-term survival in most patients, radiation-induced late toxicity is of particular concern, and strategies to minimize late effects are important. There has been increasing recognition that radiotherapy for head and neck cancer can bring about premature arteriosclerosis in the carotid arteries and consequent cerebrovascular events.

Table 1. Dose (Gy) to carotid arteries and spinal cord for the 10 patients

Organs at risk	Lateral parallel pair[a]	Anterior oblique[a]	*p*-value
Right carotid			
Average of maximum dose	51.08 (50.67–51.48)	42.25 (37.88–46.62)	0.0027
Average of mean dose	36.53 (33.20–39.85)	20.65 (18.30–23.00)	<0.0001
Left carotid			
Average of maximum dose	51.11 (50.72–51.51)	41.93 (38.01–45.84)	0.0011
Average of mean dose	37.53 (35.10–39.97)	21.86 (19.34–24.38)	<0.0001
Spinal cord			
Average of maximum dose	3.16 (2.41–3.91)	18.89 (16.97–20.81)	<0.0001

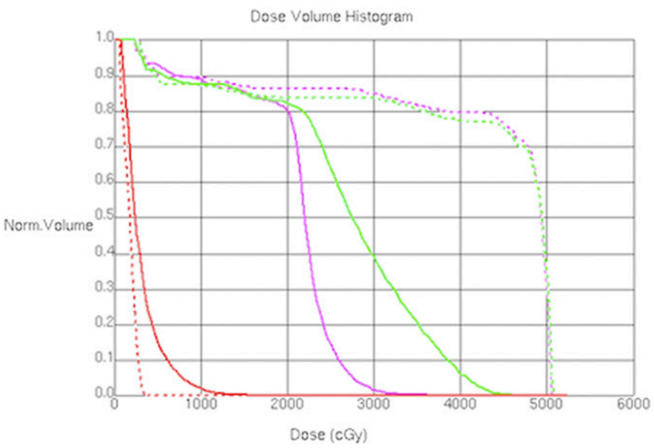
[a]95% confidence interval of the average.

Stroke is a major cause of mortality and morbidity in the general population with an annual UK incidence of approximately 150,000 cases. In 2010, stroke was the fourth leading cause of death after cancer, heart disease and respiratory disease. More than half of patients who survive a stroke will be dependent on others for activities of daily living.[3] Well-documented risk factors for ischaemic stroke include hypertension, smoking, diabetes, atrial fibrillation, hypercholesterolaemia, increased alcohol intake, poor diet and obesity. 85% of strokes are due to cerebral infarction and 50% of these are due to atherosclerosis in major arteries,[4] *e.g.* common carotid artery, internal carotid artery, vertebral arteries and the circle of Willis.

A pooled prevalence of asymptomatic carotid artery stenosis in the general population has been reported as being 4.2% for moderate (≥50%) and 1.7% for severe (≥70%) stenosis.[5,6]

It has been known for more than a century that radiation can lead to vascular injury. The mechanism by which damage occurs is thought to involve an inflammatory reaction whereby a combination of pro-inflammatory cytokines, macrophages and growth factors lead to proliferation and an increase in the intima–media thickness (IMT) of the vessel wall. There is also associated atrophy of smooth muscle cells, development of fibrosis, necrosis, obliteration of the adventitial vasa vasorum and accelerated atherosclerosis. The consequences of accelerated atherosclerosis include vascular occlusion, progressive arterial stenosis, thrombosis and arterial rupture.[7–10] Angiographic findings of radiation-induced accelerated carotid atherosclerosis are that the lesions are typically longer than traditional atherosclerotic lesions, occur within the radiation portal and the points of maximal stenosis tend to be at the ends of the stenotic area.[11]

Figure 2. Dose–volume histogram for lateral parallel opposed fields (dotted lines) and for anterior oblique fields (solid lines). Right carotid is represented by green lines, left carotid by purple lines and spinal cord by red lines. Norm., normalized.

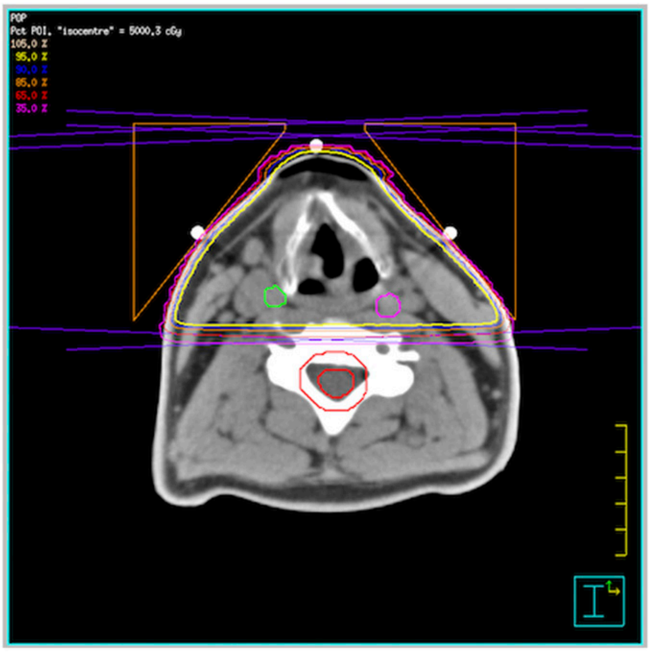


Over the past three decades, there has been an increasing number of published studies that have reported a link between radiotherapy to the neck and stroke or carotid artery stenosis. A MEDLINE® search using keywords including "radiotherapy", "head and neck neoplasms", "stroke" and "carotid artery diseases" and "carotid stenosis" produced 9 titles before 1990, 18 between 1990 and 1999 and 48 from 2000 to the present time, including 20 published in the past 5 years.

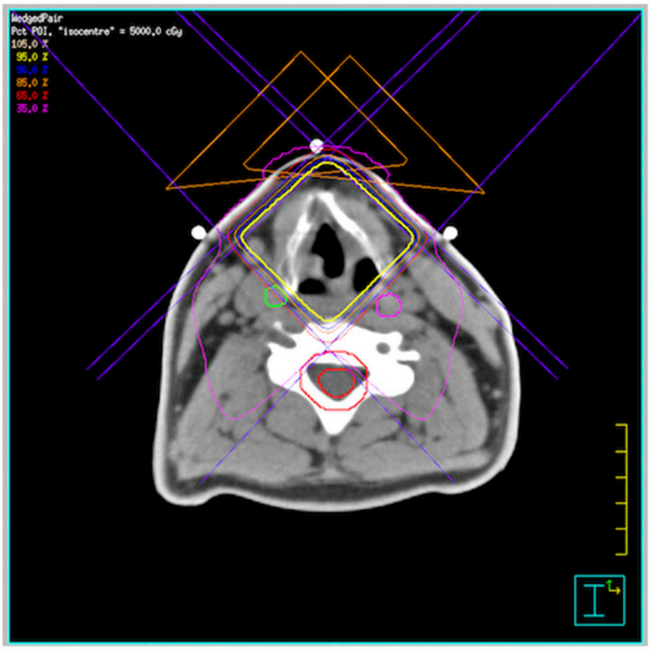
Many of these studies report a significantly increased relative risk of stroke in patients who received radiotherapy to the head and/or neck. Table 2 summarizes studies identified by the MEDLINE search and published since 2000 which have quantified the risk. It is notable that the majority of these studies do not include early glottic cancers, where the irradiated segment of carotid artery is more limited. However, a recent publication by Swisher-McClure et al[25] specifically compared the risk of fatal cerebrovascular accident (CVA) amongst patients with Stage I glottic cancer treated with radiotherapy or surgery and found a small increased risk of fatal CVA in the radiotherapy group (2.8% *vs* 1.5% at 15 years).

Scott et al[26] and Plummer et al[27] have both published reviews of the subject, not only concluding that head and neck irradiation does increase the risk of cerebrovascular events but also highlighting some of the difficulties in discerning the clinical significance of these findings. The obvious question is whether there is evidence of a dose effect or threshold dose above which cerebrovascular events are more likely. There appears to be much heterogeneity within and between the studies in terms of radiation technique, dose and fraction size, making it difficult to

Figure 3. Field arrangement for lateral parallel opposed fields (a) and for anterior oblique fields (b). The right carotid artery is contoured in green and the left carotid artery in pink.



(a)



(b)

draw any conclusions. Although the data could be "normalized" using a biologically equivalent dose calculation, many studies do not provide enough detail to allow this.

However, some individual studies have suggested that there is evidence for a dose effect.[15,23,28] Dorth et al[28] reported a hazard ratio for carotid artery stenosis of 1.4 for every 10-Gy increase in mean radiation dose in patients who received radiotherapy for locally advanced head and neck cancer. Moser et al[15] studied the risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma and reported in a subgroup analysis that the standardized incidence ratio (SIR) for stroke increased with increasing dose of radiation, giving an SIR of 0.7 for ≤30 Gy, 2.2 for 30–40 Gy and 8.6 for >40 Gy. As discussed above, a feature of radiation-induced vascular damage is an increase in the IMT. Martin et al[23] reported that there was a significant increase in the IMT in irradiated arteries, but only for doses >35 Gy.

Other studies[20,29] have found that patients who had post-operative radiotherapy had no higher risk of stroke than those who had surgery alone, suggesting that the lower radiation doses used in the post-operative setting may be relevant.

The current ARTFORCE trial protocol[30] stipulates that the carotid arteries (in a high-dose area) are contoured as an organ at risk and should receive <70 Gy.

Establishing a suitable control group for these studies is problematic. Some studies[23,24] used the contralateral unirradiated carotid as a control; however, this vessel would still have received a low dose of radiation which may be relevant. Other groups have used data from general population databases[12] which may not be representative as many patients with head and neck cancer already have the aforementioned "standard" risk factors for cerebrovascular disease.

These cerebrovascular events in question are late effects, sometimes occurring more than 15 years after radiotherapy.[12,24,27] Consequently, it can be difficult to be certain that the events are due to previous radiotherapy and not simply due to effects of increasing age in an "at risk" population.

One study described how the rate of carotid stenosis increased with increasing time after radiation,[24] with the event rate being low for the first 10 years, increasing to 4.8 and 21.3 events per 100 person-years for the periods 10–15 years and more than 15 years after radiotherapy, respectively. Dorresteijn et al[12] reported that the risk of cerebrovascular events increases over time, with a relative risk of 10.1 at 10-year follow-up. In many other disease sites, a late effect occurring 15 years after treatment is unlikely to be clinically significant as there will be few survivors, but the very favourable 5-year local control and mortality rates for T1 glottic cancer are such that large numbers of patients will be cancer free and at risk of toxicity from late effects. In addition, many of these patients will already have one or more of the "standard" risk factors for cerebrovascular events, further increasing their risk.

Strategies to minimize the risk of carotid artery stenosis and cerebrovascular events include modification of the well-established risk factors such as controlling hypertension and hypercholesterolaemia, smoking cessation, weight reduction and improved diet. There has been recent interest in the use of serum and imaging biomarkers to detect the early development of atherosclerosis.[31] In the light of increasing evidence that exposure of the carotid arteries to radiation is an independent risk factor, attention has also turned to methods of reducing this exposure.

Table 2. Relative risk of cerebrovascular events

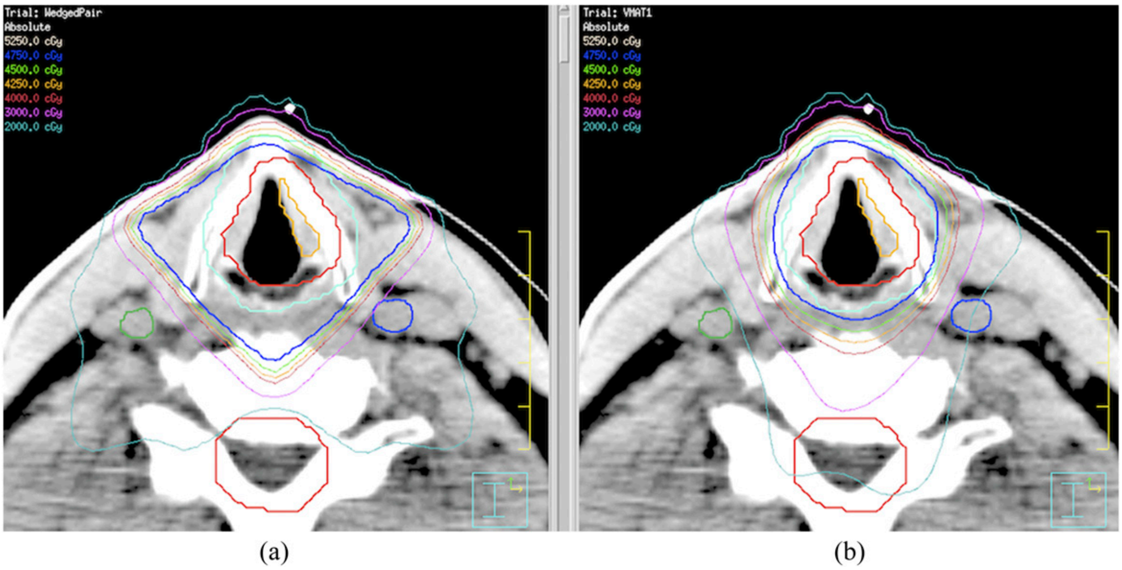
Date	Study	No. of patients	Cancer	Site treated	Control arm	Total dose (Gy)	Dose/ fraction	BED_3 (Gy)	Risk of stroke (95% confidence interval)
2002	Dorresteijn et al[12]	367	H&N	H&N	GP	50–66	2.0–2.4	≥83	RR, 5.6 (3.1–9.4)
2005	Bowers et al[13]	1926	HL	Mantle	Siblings	40	NS	N/A	RR, 5.62; $p < 0.0001$
2006	Jagsi et al[14]	820	Breast	SCF	GP	NS	NS	N/A	HR, 2.8; $p = 0.021$
2006	Moser et al[15]	476	NHL	Neck	GP	28–60	NS	N/A	SIR, 2.3 (1–4.5)
2009	De Bruin et al[16]	2201	HL	N&M	No RT	36–44	2	60–73.3	HR, 2.2 (0.7–7)
2011	Huang et al[17]	9738	H&N	H&N	Nil	NS	NS	N/A	HR, 2.18 (1.43–3.35)
2002	Haynes et al[18]	413	H&N	H&N	GP	64	NS	N/A	RR, 2.09; $p = 0.0007$
2011	Lee et al[19]	1094	NPC	H&N	Appendectomy patients	NS	NS	N/A	HR, 1.66 (1.16–2.86)[a] HR, 0.87 (0.56–1.33)[b]
2008	Smith et al[20]	6862	H&N	H&N	Surgery alone	NS	NS	N/A	HR, 1.59; $p = 0.0005$
2006	Hooning et al[21]	4259	Breast	SCF/ IMC	GP	40 50	15 25	75.5 83.3	HR, 1.0 (0.7–1.6)
2006	Woodward et al[22]	5752	Breast	SCF	Breast only	NS	NS	N/A	HR 1.0 (0.6–1.6)
2005	Martin et al[23]	40	H&N	H&N	Contralateral carotid	30–60	10–25	52.5–101	14 *vs* 5 cases carotid artery stenosis; $p = 0.03$
2005	Brown et al[24]	44	H&N	Neck	Contralateral carotid	30–75	5–39	≥72	18% *vs* 7% incidence carotid artery stenosis; $p = 0.13$
2013	Swisher-McClure et al[25]	8721	Glottis	Larynx	Surgery	NS	NS	N/A	Cumulative incidence fatal cerebrovascular accident 2.8% *vs* 1.5% at 15 years; $p = 0.024$

BED, biologically equivalent dose; GP, general population; HL, Hodgkin lymphoma; H&N, head and neck; HR, hazard ratio; IMC, internal mammary chain; N/A, not applicable; NHL, non-Hodgkin lymphoma; N&M, neck and mediastinum; NPC, nasopharyngeal cancer; NS, not stated; RR, relative risk; RT, radiotherapy; SCF, supraclavicular fossa; SIR, standardized incidence ratio.
[a]Age 35–54 years.
[b]Age, 55–64 years.

Chera et al[32] found that intensity-modulated radiotherapy (IMRT) significantly reduced the dose to the carotid arteries (median carotid dose with unilateral target 4 Gy with IMRT, 19 Gy with 3D conformal radiotherapy and 39 Gy with an opposed lateral technique). The potential pitfalls of IMRT in this situation include the problem of generating "hot spots" within the larynx, which may subsequently compromise organ function, geographical miss due to swallowing-related organ movement (up to 20–25 mm craniocaudally and 3–8 mm anteroposteriorly) and also the overcomplication of what has traditionally been a simple and effective treatment.

Another approach is to adopt an alternative beam arrangement to spare the carotid arteries. As demonstrated in our study, the anterior oblique field arrangement is associated with a 43% reduction in the mean dose received by the carotid arteries

Figure 4. Dose distribution with an anterior oblique wedged pair (a) *vs* volumetric-modulated arc therapy optimized to spare the carotids (b). Gross tumour volume outlined in orange, clinical target volume in red, planning target volume in turquoise, right carotid artery in green and left carotid artery in blue.



(21 Gy with anterior oblique fields compared with 37 Gy with a parallel opposed pair of lateral fields).

To illustrate the dosimetric differences between an anterior oblique wedged pair and IMRT techniques, one case of a T1a left vocal cord squamous cell carcinoma was also planned using single arc volumetric-modulated arc therapy (VMAT). The gross tumour volume (GTV) was defined as the left vocal cord tumour. The clinical target volume was created by expanding the GTV by 0.5 cm, then editing to include the entire left vocal cord, the right vocal cord with no margin and the contralateral arytenoid was spared. The planned volume was first optimized to limit the dose received by the carotid arteries (Figure 4). The mean doses to the left and right carotid arteries were 15.1 and 12.2 Gy, respectively, compared with 17.1 and 16.1 Gy using an anterior oblique wedged pair approach. As expected, the spinal cord dose was increased (14 Gy *vs* 5.25 Gy) but remained within tolerance. A second optimization was performed, which resulted in a hybrid of dose distributions between the anterior oblique arrangement and the initial VMAT plan (Figure 5). The additional degrees of freedom afforded by VMAT allowed for optimization of the treatment plan and reduction in doses to the carotid arteries or spinal cord. The homogeneity of the dose distribution was acceptable with both the anterior oblique wedged pair and VMAT plans, with equivalent point maximum doses of 105%.

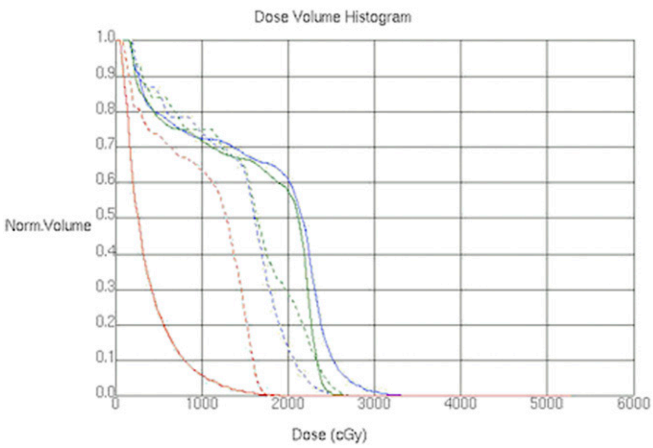
CONCLUSION

It is predictable that an anterior oblique field arrangement will yield a lower radiation dose to the carotid arteries than a parallel pair arrangement. The main objective of this study was to quantify the potential reduction in dose to the carotids and to review the evidence for increased risk of vascular events due to irradiation of the carotids. We acknowledge that a major limitation of the literature reviewed is that few of these studies included early glottic cancers. It therefore remains unclear whether the apparent increased risk of vascular damage seen in these studies can be applied when a much smaller segment of carotid artery is irradiated during the treatment of early glottic cancer.

There is some evidence that newer techniques such as IMRT/VMAT are better able to spare the carotid arteries, accepting the potential drawbacks as described above.

The anterior oblique technique has been used as a standard in our centre for decades and has previously been shown to be safe and effective.[1] This study has demonstrated that this simple field arrangement is associated with a significantly lower mean dose to the carotid arteries than that to the lateral parallel pair. We recognize that this technique does result in a smaller treated volume but are confident that this does not compromise tumour coverage as our local control rates are consistently above 90%.

Figure 5. Dose–volume histogram for anterior oblique wedged fields (solid lines) and for volumetric-modulated arc therapy (dotted lines). Right carotid is represented by green lines, left carotid by blue lines and spinal cord by red lines. Norm., normalized.



These patients have an excellent prognosis, and all steps should be taken to minimize the risk of developing cerebrovascular complications as a late consequence of irradiation.

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