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Improved Normal Tissue Sparing in Head and Neck Radiotherapy Using Biological Cost Function Based-IMRT

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Intensity-modulated radiotherapy (IMRT) has reduced the impact of acute and late toxicities associated with head and neck radiotherapy. Treatment planning system (TPS) advances in biological cost function based optimization (BBO) and improved segmentation techniques have increased organ at risk (OAR) sparing compared to conventional dose-based optimization (DBO). A planning study was undertaken to compare OAR avoidance in DBO and BBO treatment planning. Simultaneous integrated boost treatment plans were produced for 10 head and neck patients using both planning systems. Plans were compared for target coverage and OAR avoidance. Comparisons were made using the BBO TPS Monte Carlo dose engine to eliminate differences due to inherent algorithms. Target coverage (V95%) was maintained for both solutions. BBO produced lower OAR doses, with statistically significant improvement to left (12.3%, $p = 0.005$) and right parotid mean dose (16.9%, $p = 0.004$), larynx V50 Gy (71.0%, $p = 0.005$), spinal cord (21.9%, $p < 0.001$) and brain stem dose maximums (31.5%, $p = 0.002$). This study observed improved OAR avoidance with BBO planning. Further investigations will be undertaken to review any clinical benefit of this improved planned dosimetry.

Key words: Biological cost functions; Dose avoidance; Head and neck cancer; Intensity-modulated radiotherapy (IMRT); Monte Carlo algorithms.

Introduction

Radiotherapy is a proven modality in providing local regional control and improving survival outcomes in head and neck cancer patients (1, 2). Intensity modulated radiation therapy (IMRT) reduces treatment related toxicities through the creation of steep dose gradients at the target and organ at risk (OAR) interface, as well as modulating dose to avoid OARs that are located within the concavities of irregularly shaped targets (3-5). Delivering highly conformal doses to target volumes, while maintaining and improving critical structure avoidance, is significantly improved with IMRT planning and treatment delivery (6-9). Yet head and neck IMRT continues to present planning challenges with numerous dose limiting structures neighboring tumors within this anatomical site. This has led to multiple evaluations assessing OAR avoidance with IMRT (10, 11). Recent developments in radiotherapy treatment planning systems (TPS) have seen the introduction of biological cost function based optimization (BBO). This approach enables inverse planned IMRT using prescriptions based on biological cost

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Abbreviations: TPS: Treatment Planning System; IMRT: Intensity Modulated Radiation Therapy; OAR: Organ at Risk; EUD: Equivalent Uniform Dose; SIB: Simultaneous Integrated Boost; GTV: Gross Tumor Volume; CTV: Clinical Target Volume; PTV: Planning Target Volume.

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functions as well as, or instead of conventional DVH constraints. Biological cost functions are based on equivalent uniform doses (EUD's) rather than physical dose constraints such as maximum and minimum dose, or points on a dose-volume histogram (DVH). They include cost functions based on serial and parallel complication models, where the optimizer minimizes the EUD to the OAR in its entirety. BBO has also been combined with a number of other improved planning techniques compared to traditional dose-based optimization (DBO), including constrained fluence optimization and constrained aperture optimization. An efficient Monte Carlo (MC) dose calculation is used by the BBO TPS, enabling increased dose accuracy (compared to DBO's superposition (SP) algorithms) within a clinically acceptable calculation time (12). Combining these features, the anticipated OAR dose reduction may lead to improved planned dosimetry and improved quality of life for this patient group (13, 14). Numerous planning studies have provided a comparison of commercial treatment planning systems (15, 16). Semenenko *et al.* provided a dosimetric comparison of commercially available BBO and DBO TPS utilizing each systems' inherent calculation algorithm (15). Our study aimed to extend the findings of Semenenko, to not only derive the potential benefits of BBO in the head and neck, but the potential dosimetric impact on multiple structures when different algorithms are utilized. A planning study was undertaken to compare the optimization techniques of one commercially available DBO TPS and one BBO TPS. Further to this, each DBO plan was recalculated using a like Monte Carlo calculation algorithm, to gain a true dose discrepancy and any subsequent dosimetric impact through removing any bias associated with different calculation engines.

Methods and Materials

In this institutional ethics approved study, treatment plans were produced for ten consecutive patients with histologically confirmed squamous cell carcinoma (SCC) of the head and neck deemed clinically suitable for curative radiotherapy with IMRT. Two patients presented with 'Mx' disease, and were treated radically accordingly. Treatment plans clinically accepted and delivered with DBO using the XiO v4.33.02 TPS (Elekta CMS Software, St Louis, MO, USA) were generated on BBO using the Monaco v1.0.2 TPS (Elekta CMS Software, St Louis, MO, USA) for plan comparison with the previously accepted DBO plans.

Patient demographics, tumor and treatment characteristics are shown in Table I. The prescribed doses were planned via a simultaneous integrated boost (SIB), to a gross tumor volume (GTV) or tumor bed for post-operative radiation therapy (all referred to as GTV in this article), high risk clinical target volume (CTV) and low risk CTV. Dose to GTV (60-70 Gy), high risk CTV (60-63 Gy) and low risk CTV (54-56 Gy) was

Table I
Patient and tumor characteristics.

Characteristics	No. of patients
Gender	
Male	9
Female	1
Age (Mean)	
Male	61
Female	54
Primary Tumor Site	
Larynx	
Supraglottic	2
Transglottic	1
Nasopharynx	1
Oral Cavity	
Tongue Base	2
Floor of Mouth	1
Tonsillar Fossa	1
Oropharynx	1
Unknown Primary	1
T-stage	
T1	1
T2	3
T3	3
T4	2
Tx	1
N-stage	
N0	3
N1	2
N2a	1
N2b	2
N2c	2
M-stage	
M0	8
MX	2
*Dose Prescription	
70/63/56	6
70/63/54	1
66/60/54	1
64/60/54	1
60/54	1

Abbreviations: T = Tumor; N = Node; M = Metastases.

*Dose Prescription: *i.e.* 70/63/56 = Dose (Gy) to PTV₁/Dose (Gy) to PTV₂/Dose (Gy) to PTV₃.

planned at 5 fractions per week over 6 to 7 weeks. Dose prescription was dependent on clinical intent (*i.e.* definitive/post-operative). This study aimed to incorporate the spectrum of head and neck cases seen in a normal radiotherapy department, hence, the variety in dose prescription. It is hoped this would provide generalizable results to a normal head and neck cancer treatment population. Each target was expanded with a 1 cm GTV-CTV margin, and a further 0.5 cm margin to form PTV₁, PTV₂ and PTV₃ respectively.

Optimized IMRT plans, deliverable via 7 equally spaced step-and-shoot segmented beams on a 6MV linear accelerator (Elekta Synergy, Elekta Oncology, Crawley, UK), were

generated using both planning systems on 0.25 cm computed tomography slices. DBO plans were calculated using a Multigrad Superposition algorithm (17). Dose is computed by convolving the total energy released through Monte Carlo-generated energy deposition kernels (18). 0.2cm grid spacing was used in the DBO plans. BBO plans were calculated using a MC calculation algorithm (XVMC/VEF- 2% variance and 0.3 cm) as described and validated by Fippel *et al.* (12, 19, 20). Benchmarking of this MC algorithm against the BEAM Monte Carlo code has also occurred (21). This was previously noted by Semenenko *et al.* (15). Software limitations in the Monaco v1.0 didn't allow for calculation with 0.2cm grid spacing.

A set of institutional dose goals (Table II) were used as a criteria for plan acceptability. One prescribing radiation oncologist, in conjunction with the afore mentioned dose goals, determined clinical acceptability of the plan via isodose review following plan derivation. Competing plans utilized the same isocentre location and beam angles.

Segmented DBO plans were recalculated using the Monte Carlo dose algorithm of the BBO TPS (without changing monitor units, 0.3 cm grid spacing), and the resulting isodoses and DVHs compared with those produced via BBO and segmentation. This allowed an isolated comparison of the effects of the planning systems' optimization and segmentation techniques, by eliminating differences in the inherent dose calculation algorithms and grid spacing of the different planning systems. This also enabled an isolated demonstration of the differences between the DBO TPS's SP algorithm and the BBO TPS's MC algorithm.

Doses were assessed and compared for all the nominated target volumes and OARs. Mean values were calculated for all ten patients. For quantitative plan comparison, institutional dose goals were used in combination with V20% (of highest prescription dose), V15%, V10%, and V5% to the entire patient image dataset, to assess integral dose to healthy tissue. Homogeneity and conformity indices were also compared. Homogeneity Index (HI) is defined as the quotient of the maximum dose within the target to the highest prescription dose, *i.e.* . A value closer to 1 indicates better

dose homogeneity. The conformity indices (CI) describes the conformation of dose to targets, and is defined as the quotient of the treated volume to the volume of the PTV (22). The treated volume in this study was taken as V95%, *i.e.* $CI = \frac{V_{95\%}}{V_{PTV}}$, and was calculated for each PTV. A CI greater than 1 indicates that the 95% isodose is greater than the target volume and includes healthy tissue. Conversely, a CI less than one indicate the 95% isodose does not encompass the target volume. Although it is understood that this numerical index does not indicate spatial agreement of the 95% isodose against the target volume, isodoses were assessed by the radiation oncologist for appropriate coverage.

A matched pairs t-test between means was performed to determine the statistical significance of any discrepancies for the comparisons between the study groups.

Results

When comparing the results calculated with inherent calculation algorithms (*i.e.* DBO SP vs. BBO MC), the BBO TPS produces similar coverage for GTV and all PTVs. The CI also improves for PTV₁ and PTV₂, indicating a smaller and therefore more conformal BBO V95 (refer to Tables III and IV). Major dose reductions were seen in larynx, parotids, spinal cord and brain stem (refer to Tables V and VI).

When the DBO plans were recalculated using BBO TPS's MC algorithm, the differences shown are closer to 'true' differences, calculated using the same, more accurate algorithm, eliminating discrepancy caused by the SP and MC dose calculation algorithms.

Target coverage (Tables III and IV) was similar in both planning systems for GTV V98% (BBO: Mean = 99.1 ± 1.3%; DBO: Mean = 98.9 ± 2.2%, p = 0.894) and PTV₁ V95% (BBO: Mean = 97.4 ± 1.9%; DBO: Mean = 98.7 ± 1.7%, p = 0.079). PTV₂ (BBO: Mean = 95.7 ± 3.0%; DBO: Mean = 97.5 ± 1.9%, p = 0.009) and PTV₃ V95% (BBO: Mean = 93.9 ± 3.3%; DBO: Mean = 96.6 ± 2.5%, p = 0.004), coverage was moderately superior on the DBO plan, but still deemed clinically acceptable by the radiation oncologist.

Slightly improved DBO target coverage was at the expense of increased treated volumes and subsequent conformity indices. The 95% Conformity Indices for all targets were significantly different: PTV₁ (BBO: Mean = 1.80 ± 0.23; DBO: Mean = 2.53 ± 0.37, p = 0.001), PTV₂ (BBO: Mean = 1.67 ± 0.40; DBO: Mean = 2.23 ± 0.45, p = 0.002) and PTV₃ (BBO: Mean = 1.40 ± 0.18; DBO: Mean = 1.50 ± 0.16, p = 0.047). The HI of both the DBO (Mean = 1.15 ± 0.05) and BBO (Mean = 1.13 ± 0.07) plans

Table II
Target coverage and OAR dose goals.

Target	Constraint	OAR	Constraint
GTV	V98% ≥ 98%	Brainstem	D _{max} ≤ 54 Gy
PTV ₁	V95% ≥ 95%	Spinal Cord	D _{max} ≤ 45 Gy
PTV ₂	V95% ≥ 95%	Parotid	D _{mean} ≤ 26 Gy,
		Glands	V30Gy < 50%
PTV ₃	V95% ≥ 95%	Larynx	V50Gy < 33%
		Mandible	D _{max} ≤ 70 Gy

Abbreviations: D_{max} = Dose Maximum; D_{mean} = Dose Mean.

Table III
Mean, standard deviation and range for target volumes, conformity indices and homogeneity.

Dose parameter	DBO Superposition (SP)	DBO Monte Carlo (MC)	BBO Monte Carlo (MC)
Target volumes	Mean \pm SD (range)	Mean \pm SD (range)	Mean \pm SD (range)
GTV V98% (%)	96.9 \pm 4.1 (99.5–85.5)	98.9 \pm 2.2 (100–93.1)	99.1 \pm 1.3 (100–96.0)
PTV ₁ V95% (%)	97.1 \pm 3.2 (100–91.1)	98.7 \pm 1.7 (100–94.9)	97.4 \pm 1.9 (99.1–93.6)
PTV ₂ V95% (%)	96.4 \pm 3.0 (100–90.7)	97.5 \pm 1.9 (99.8–93.2)	95.7 \pm 3.0 (98.8–89.4)
PTV ₃ V95% (%)	93.4 \pm 3.7 (97.6–84.1)	96.6 \pm 2.5 (98.9–90.7)	93.9 \pm 3.3 (98.4–87.3)
HI	1.10 \pm 0.03 (1.14–1.05)	1.15 \pm 0.05 (1.29–1.10)	1.13 \pm 0.07 (1.30–1.08)
Conformity indices 95%			
PTV ₁	2.01 \pm 0.22 (2.33–1.61)	2.53 \pm 0.37 (3.40–2.11)	1.80 \pm 0.23 (2.12–1.45)
PTV ₂	1.80 \pm 0.32 (2.28–1.29)	2.23 \pm 0.45 (2.75–1.54)	1.67 \pm 0.40 (2.24–1.12)
PTV ₃	1.36 \pm 0.13 (1.57–1.19)	1.50 \pm 0.16 (1.77–1.27)	1.40 \pm 0.18 (1.63–1.12)

Abbreviations: DBO SP = Dose-based optimization planned with superposition algorithm; DBO MC = Dose-based optimization recalculated with Monte Carlo algorithm; BBO MC = Biologically-based optimization planned with Monte Carlo algorithm; SD = Standard Deviation; HI = Homogeneity Indices.

were not significantly different ($p = 0.382$) indicating comparable dose maximums of both planning systems.

There was a statistically significant reduction in high dose regions to the spinal cord and brain stem. BBO plans demonstrated a 21.9% spinal cord D1% reduction (BBO: Mean: 32.8 ± 1.5 ; DBO Mean: 41.9 ± 2.7 , $p < 0.001$), and 31.5% brain stem D1% reduction (BBO: Mean = 22.9 ± 14.3 ; DBO: Mean = 32.7 ± 13.8 , $p = 0.002$).

Bilateral parotid mean dose was also significantly reduced with BBO. Left parotid (BBO: Mean = 20.3 ± 2.5 Gy; DBO: Mean = 23.2 ± 3.0 Gy, $p = 0.005$) presented a 12.3% improvement, and right parotid (BBO: Mean = 25.1 ± 5.5 Gy; DBO: Mean = 30.2 ± 6.6 Gy, $p = 0.004$) a 16.9% improvement. V30Gy of left (BBO: Mean = 24.7 ± 6.4 %; DBO: Mean = 30.8 ± 6.6 %, $p = 0.011$) and right (BBO: Mean = 33.9 ± 8.9 %; DBO: Mean = 43.5 ± 12.6 %,

$p = 0.042$) parotids demonstrated substantial improvement in the BBO plans.

V50Gy of the larynx presented the most substantial reduction in dose with BBO. In the six patients where laryngectomy hadn't occurred, or larynx wasn't directly encompassed by/ involved in a high dose target volume, BBO delivered a 71% reduction ($p = 0.005$).

Integral dose was significantly improved at multiple dose levels with BBO. V20% of highest prescribed dose delivered 8.0% improvement ($p < 0.001$), and V15%, V10% and V5%, a 10.5% ($p < 0.001$), 12.2% ($p < 0.001$) and 10.7% ($p < 0.001$) improvement respectively.

BBO derived plans generated an 11.3% increase in segments per treatment plan (BBO: Mean = 124.8 ± 19.6 ; DBO: Mean = 112.3 ± 20.3 %, $p = 0.079$).

Table IV
Percentage difference and p-values of plan discrepancy.

Dose parameter	DBO SP – BBO MC	DBO MC – BBO MC	DBO SP – DBO MC
Target volumes	% diff (p-value)	% diff (p-value)	% diff (p-value)
GTV V98% (%)	-2.1 (0.192)	-0.1 (0.894)	2.1 (0.023)
PTV ₁ V95% (%)	-0.4 (0.671)	1.3 (0.079)	1.7 (0.068)
PTV ₂ V95% (%)	0.8 (0.101)	1.9 (0.009)	1.1 (0.055)
PTV ₃ V95% (%)	-0.6 (0.476)	2.9 (0.004)	3.3 (<0.001)
HI	-2.3 (0.237)	1.9 (0.382)	-4.5 (0.004)
Conformity indices 95%			
PTV ₁	10.7 (0.088)	28.9 (0.001)	-25.6 (<0.001)
PTV ₂	7.4 (0.172)	25.2 (0.002)	-23.7 (<0.001)
PTV ₃	-2.9 (0.357)	6.7 (0.047)	-10.3 (<0.001)

Abbreviations: DBO SP = Dose-based optimization planned with superposition algorithm; DBO MC = Dose-based optimization recalculated with Monte Carlo algorithm; BBO MC = Biologically-based optimization planned with Monte Carlo algorithm; HI = Homogeneity Indices.

Table V
Mean, standard deviation and range for OAR and normal tissue irradiated volume.

Dose parameter	DBO Superposition (SP)	DBO Monte Carlo (MC)	BBO Monte Carlo (MC)
OAR	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)
Brain Stem D _{max} (Gy)	34.5 ± 14.2 (51.3–10.2)	34.4 ± 14.0 (52.1–10.5)	26.4 ± 15.3 (42.8–4.0)
Brain Stem D1% (Gy)	30.6 ± 13.4 (49.4–8.8)	32.7 ± 13.8 (49.2–9.4)	22.9 ± 14.3 (40.3–3.9)
Brain Stem D2% (Gy)	28.8 ± 13.4 (48.3–7.2)	32.0 ± 13.9 (48.4–7.6)	21.9 ± 14.1 (39.4–3.7)
Spinal Cord D _{max} (Gy)	42.7 ± 1.6 (45.1–40.2)	43.6 ± 2.5 (48.2–40.1)	36.1 ± 1.4 (38.3–33.3)
Spinal Cord D1% (Gy)	40.0 ± 2.2 (43.6–36.5)	41.9 ± 2.7 (47.0–37.2)	32.8 ± 1.5 (35.7–30.7)
Spinal Cord D2% (Gy)	39.3 ± 2.4 (42.8–35.3)	41.1 ± 2.8 (45.7–36.0)	31.8 ± 1.8 (35.1–29.5)
Rt Parotid D _{mean} (Gy)	28.3 ± 6.5 (36.1–19.9)	30.2 ± 6.6 (38.0–21.8)	25.1 ± 5.5 (33.7–17.1)
Rt Parotid V30Gy (%)	39.9 ± 10.6 (55.2–21.5)	43.5 ± 12.6 (68.0–23.7)	33.9 ± 8.9 (46.7–20.9)
Lt Parotid D _{mean} (Gy)	22.5 ± 2.9 (27.1–18.4)	23.2 ± 3.0 (28.3–19.3)	20.3 ± 2.5 (25.8–16.3)
Lt Parotid V30Gy (%)	30.3 ± 6.7 (40.0–17.9)	30.8 ± 6.6 (41.3–20.4)	24.7 ± 6.4 (33.4–14.5)
Larynx V50Gy (%)	24.3 ± 8.9 (38.0–11.9)	29.7 ± 12.9 (46.3–12.6)	8.6 ± 5.1 (7.8–4.3)
Mandible D _{max} (Gy)	70.7 ± 6.8 (78.6–58.2)	71.9 ± 5.2 (78.2–60.5)	71.6 ± 6.1 (78.5–58.7)
Mandible D1% (Gy)	67.9 ± 6.9 (76.6–55.0)	70.0 ± 7.1 (78.6–55.2)	67.4 ± 5.8 (73.6–56.1)
Mandible D2% (Gy)	65.8 ± 7.1 (76.2–54.1)	69.8 ± 7.5 (79.1–54.0)	65.9 ± 5.8 (72.9–55.3)
*Irradiated volume (cc)			
V20%	4165 ± 779 (5823–3345)	4287 ± 806 (5999–3433)	3943 ± 771 (5717–3041)
V15%	4647 ± 842 (6402–3747)	4776 ± 855 (6580–3853)	4275 ± 822 (6115–3278)
V10%	5283 ± 901 (7201–4271)	5461 ± 9364 (7461–4439)	4794 ± 905 (6777–3665)
V5%	6246 ± 1070 (8456–5016)	6613 ± 1153 (8924–5261)	5906 ± 1123 (8197–4398)

Abbreviations: DBO SP = Dose-based optimization planned with superposition algorithm; DBO MC = Dose-based optimization recalculated with Monte Carlo algorithm; BBO MC = Biologically-based optimization planned with Monte Carlo algorithm; SD = Standard Deviation; D_{max} = Dose maximum; D_{mean} = Dose mean; D1%/2% = Dose (Gy) to 1%/2% of Volume; OAR= Organ at Risk.

*Irradiated volume (cc) = Volume of healthy tissue receiving integral dose *i.e.* V20% = 20% of maximum prescribed dose.

Discussion

The benefits of IMRT planning for head and neck cancers have been demonstrated based on both planning and clinical outcome studies including an early report from a randomized study (23). Improved OAR sparing with reduced radiation related side-effects have been documented. This retrospective planning study has examined the benefits of utilizing a new planning system based on biological cost functions with improved optimization and segmentation techniques, for inverse IMRT planning of complex head and neck cases. While similar planning studies have reported the benefits of the BBO TPS (15), our dose comparison utilizing the same Monte Carlo calculation engine provides grounds for a truer comparison, through the removal of factors inherent to each system. It also quantifies algorithm discrepancy, highlighting the potential dosimetric ramifications when alternate algorithms are utilized. This aspect has not been assessed in previous publications.

Equivalent uniform dose (or EUD) provides the theoretical basis for planning in the assessed BBO TPS. Niemierko

initially introduced the concept of EUD as the biological equivalent dose that if given uniformly, will lead to the same cell kill in the tumor as the actual non-uniform dose distribution (24). Applied clinically, this theory dictates that the presence of a cold spot within a target would have a significant impact on the likelihood of tumor control. This is an aspect not necessarily quantified in traditional dose-volume based objectives. The basis for this understanding of EUD was later applied to normal tissue.

EUD-based objective functions, as described by Wu *et al.*, rely heavily on three generally accepted concepts, in which (a) tumor control is a function of dose minimum to the tumor, (b) the biological response of serial functioning normal tissue is a function of dose maximum, and (c) parallel normal tissue have a biologic response more closely associated with mean dose (25). The BBO TPS utilizes a set of EUD-based objective functions based on these principles. The Poisson Cell Kill Cost Function works to eradicate cold spots within the target to enhance tumor control. The Serial and Parallel Cost Functions work on the dose maximum and mean respectively to ascertain the appropriate biological response.

Table VI
Percentage difference and p-values of plan discrepancy.

Dose parameter	DBO SP – BBO MC	DBO MC – BBO MC	DBO SP – DBO MC
OAR	% diff (p-value)	% diff (p-value)	% diff (p-value)
Brain Stem D _{max} (Gy)	22.1 (0.006)	23.4 (0.005)	0.1 (0.781)
Brain Stem D1% (Gy)	25.0 (0.011)	29.9 (0.002)	-6.5 (0.011)
Brain Stem D2% (Gy)	23.9 (0.022)	31.5 (0.002)	-10.0 (0.017)
Spinal Cord D _{max} (Gy)	16.2 (<0.001)	17.2 (<0.001)	-2.0 (0.042)
Spinal Cord D1% (Gy)	18.2 (<0.001)	21.9 (<0.001)	-4.5 (<0.001)
Spinal Cord D2% (Gy)	19.0 (<0.001)	22.6 (<0.001)	-4.4 (<0.001)
Rt Parotid D _{mean} (Gy)	11.3 (0.040)	16.9 (0.004)	-6.8 (<0.001)
Rt Parotid V30Gy (%)	15.1 (0.094)	21.9 (0.042)	-9.0 (0.008)
Lt Parotid D _{mean} (Gy)	9.6 (0.016)	12.3 (0.005)	-3.0 (0.005)
Lt Parotid V30Gy (%)	18.2 (0.018)	19.8 (0.011)	-1.8 (0.266)
Larynx V50Gy (%)	64.6 (0.002)	71.0 (0.005)	-22.1 (0.054)
Mandible D _{max} (Gy)	-0.8 (0.489)	0.4 (0.810)	-1.6 (0.235)
Mandible D1% (Gy)	0.7 (0.590)	3.7 (0.006)	-3.1 (0.011)
Mandible D2% (Gy)	-0.1 (0.963)	5.7 (<0.001)	-5.8 (0.010)
*Irradiated volume (cc)			
V20%	5.3 (0.003)	8.0 (<0.001)	-2.9 (<0.001)
V15%	8.0 (<0.001)	10.5 (<0.001)	-2.8 (<0.001)
V10%	9.3 (<0.001)	12.2 (<0.001)	-3.4 (<0.001)
V5%	5.5 (<0.001)	10.7 (<0.001)	-5.9 (<0.001)

Abbreviations: DBO SP = Dose-based optimization planned with superposition algorithm; DBO MC = Dose-based optimization recalculated with Monte Carlo algorithm; OAR = Organ at Risk.

% diff = percentage difference between two planning systems/algorithm.

*Irradiated volume = volume of healthy tissue receiving integral dose *i.e.* V20% = 20% of maximum prescribed dose.

The results of this study draw parallels to that of Wu. The BBO TPS takes a similar approach to that of Wu. EUD optimization continues beyond planner-specified constraints, even once they have been met. In essence, while not understanding the ‘true’ optimal treatment plan, the EUD-based optimization provides a platform in which to converge on a better planning solution. EUD-based objectives work on the entire DVH curve, and not just the specific assigned dose request, allowing improved avoidance beyond the user-defined dose-volume levels. Utilizing the parallel-based cost function for the larynx prioritizes reduction of mid range DVH. However, the parallel-based cost function still works to reduce dose contribution at both the high and low ends of the DVH curve, whereas DBO utilizes user-defined point/s on the DVH.

EUD-based cost functions appear to minimize dose to the prioritized OAR dose. However, there is some trade-off and optimizer variability also contributing to dose avoidance. The ability of the BBO TPS to optimize throughout the segmentation process (the DBO TPS is unable to achieve this) may also contribute to OAR avoidance at low dose levels. This enables intuitive back-up jaw/MLC interactions, via reshaping/reweighting of segments to reduce MLC dose leakage. This may reduce planned low dose transmission to OARs and targets, and contribute to the lower integral dose of the BBO plans.

Finally, constrained optimization of the BBO TPS (prioritization of OAR, as opposed to unconstrained optimization in DBO where targets and OAR compete for dose) results in improved OAR avoidance at the expense of potentially larger dose hot spots in the targets. The BBO optimization prioritizes OAR dose above hot spots in target volumes. This is potentially a significant dose trade-off, and requires careful clinician consideration to assess that hot spots and dose conformity within target volumes are clinically acceptable and justify further OAR avoidance. The study was unable to objectively quantify all aspects of target dose conformity across all dose levels in competing plans. This has the potential for bias in plan assessment with this inability for objective quantification. An increase in deliverable segments in the BBO planned cohort may also have some bearing on improved treatment plan quality.

Traditional biological-based planning relies on a biological assessment of plan quality- namely in the form of tumor control probability (TCP) and normal tissue complication probability (NTCP). While the utilized BBO TPS utilizes EUD-based objective functions for plan optimization, it fails to provide a biological alternative for plan assessment. It relies on traditional dose-volume based plan analysis, and is unable to quantify the potential biological response to the

demonstrated dosimetric advantages of EUD-based objective functions in OAR avoidance.

While displaying a potential for decreased treatment efficiency, this study has demonstrated a statistically significant reduction in dose to a number of critical OARs with the use of EUD-based objectives. The potential for improved quality of life beyond cure is extremely encouraging. In particular, radiotherapy of the head and neck region is often associated with parotid gland irradiation, which can result in significant decrement in quality of life due to treatment induced xerostomia. Studies that have demonstrated a dose response relationship between xerostomia and parotid mean dose (3, 26-28) suggested 25 to 26 Gy as a planning goal to reduce the impact of parotid irradiation. BBO plans produced a reduction in mean parotid dose of approximately 12-17% (see Table VI).

With frequent 3D verification imaging, there is an increasing awareness of response related deformation in head and neck radiotherapy, revealing both parotid gland volume reduction and subsequent medial migration of the parotid glands. As a consequence, discrepancies between estimated delivered dose and planned dose can occur. Several studies have shown significant variation to planned dose as a result of parotid shrinkage (29, 30). Recent findings have reported the benefits of adaptive replanning to counteract intra-treatment parotid deformation (31, 32). Target delineation optimization and margin reduction were addressed as an effective avenue for target dose maintenance, while ensuring parotid gland dose avoidance was maintained to an acceptable level. When adaptive radiotherapy is combined with optimal planned dosimetry there presents an opportunity to maintain or further improve parotid gland avoidance.

Reduction in the inadvertent dose delivery to midline pharyngeal structures outside of the target volumes is a potentially beneficial finding of this study. A significant reduction to larynx V50Gy has the potential for not only enhanced laryngeal functional preservation, but also subsequent preservation of the swallowing structures in its immediate vicinity. Dose reduction to midline structures adjacent to target volumes may reduce both acute and late consequences of inadvertent pharyngeal axis irradiation. A number of reports have highlighted that midline avoidance can have a significant influence in the reduction of long term treatment related dysphagia (7, 8, 33-35). In an analysis of sixty six patients, Caglar *et al.* observed that laryngeal V50Gy directly correlated with aspiration and stricture complications (11). When V50Gy was less than 21%, aspiration and stricture complications were not seen. The utilization of BBO planning resulted in a larynx V50Gy dose reduction from 29.7% to 8.6%, reducing the potential incidence of complications associated with larynx irradiation.

MC dose computing algorithms, while providing greater dose calculation accuracy, will predict higher dose in both dose means and maximums, due to the statistical nature of the calculations. Results from Sakthi *et al.* (36), further reiterate the potential impact BBO in combination with MC dose computing algorithms can have in reducing dose to serial structures- namely spinal cord and brain stem in the head and neck. They calculated thirty-one head and neck plans using a conventional SP algorithm and subsequently with a MC algorithm to ascertain discrepancies between the two algorithms. MC calculated plans reported a mean increase in dose maximum to both the spinal cord and brainstem of 2.8 and 1.6% respectively. A similar dose comparison in our study, in which DBO plans were calculated using the MC algorithm and compared with an SP algorithm, yielded results in excess of those of Sakthi and colleagues. Spinal cord maximum (D2) increased by 4.4%, while brain stem (D2) increased by 10%. Perhaps of more importance is the increase to left and right parotid mean doses of 6.8 and 3.0% respectively, and the larynx V50Gy increase of 22.1%, thus further increasing the dose discrepancies between the two planning systems when utilized clinically (*i.e.* DBO with a SP algorithm, BBO with a MC algorithm). Sakthi *et al.* demonstrated similar findings for mean dose to parallel structures, including parotid glands. Such discrepancies demonstrate the potential issues associated with inherent algorithm accuracy and subsequent implications for perceived versus actual dose.

Publications from the Ghent group provide a possible reason for our dose increase from DBO SP to DBO MC (37, 38). They hypothesized that the presence of air within a given volume provides a relative reduction in particle interaction compared to surrounding tissues. Monte Carlo dose calculation engines would therefore create extra statistical noise in these air cavities- due to their ability to generate increased physical interactions- subsequently increasing dose (38). Tissue heterogeneities in the head and neck provide such interfaces, providing a basis for increased interactions in our plans. This is of particular relevance in larynx and targets, where soft tissue/air interfaces are apparent. This applies to a lesser extent to the remaining OARs.

Integral or healthy tissue dose has been a subject of review in IMRT planning and delivery (39, 40). ICRU 62 stipulates that in order to optimize conformity indices, there needs to be a dose trade off to cater for the improved target/OAR conformity associated with three-dimensional and IMRT planning *i.e.* increased integral dose to unspecified healthy tissue (41). This theory is also pursued by Purdy and colleagues (39). Whilst our study demonstrated equality in target coverage, and improvement in conformity and OAR avoidance, BBO was also able to deliver a superior result in healthy tissue avoidance at multiple dose levels (V20%, V15%, V10%, V5%)- delivering a lower integral dose to the patient.

Conclusion

This planning study was undertaken to compare OAR avoidance in DBO and BBO in head and neck treatment planning. However, it was also performed to assess the clinical validity of a treatment planning system prior to clinical implementation. There was comparable target dose coverage, with dose to the OARs significantly reduced with the BBO planning alternative. The avoidance of dose limiting structures, such as larynx and parotids, has the potential to reduce acute and late side effects that may translate into improved quality of life outcomes for the head and neck patients receiving radical radiotherapy with or without concurrent chemotherapy. While not capable of providing the magnitude of biological response, EUD-based objectives used in the BBO TPS deliver dose-volume based improvements. With ongoing improvements to plan development and efficiency, it provides a platform for improved head and neck treatment planning. Prospective collection of patient outcomes in the clinical setting, using BBO treatment planning, will be undertaken and collated to determine the potential clinical benefit in routine practice.

Conflict of Interest

We certify that regarding this paper, no actual or potential conflicts of interests exist: the work is original, has not been accepted for publication nor is concurrently under consideration elsewhere, and will not be published elsewhere without the permission of the Editor and that all the authors have contributed directly to the planning, execution or analysis of the work reported or to the writing of the paper.

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