





# Comparison of Radiation-Induced Secondary Malignancy Risk Between Sequential and Simultaneous Integrated Boost for the Treatment of Nasopharyngeal Carcinoma: Intensity-Modulated Radiotherapy versus Volumetric-Modulated Arc Therapy

This article was published in the following Dove Press journal:  
*Cancer Management and Research*

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**Purpose:** This study aimed to compare the secondary cancer risk (SCR) between the sequential boost (SEQ) technique and simultaneous integrated boost (SIB) technique in intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) in patients with nasopharyngeal carcinoma (NPC) using the concepts of organ equivalent dose (OED) and excess absolute risk (EAR).

**Patients and Methods:** IMRT-SEQ, VMAT-SEQ, IMRT-SIB, and VMAT-SIB plans were created with identical objective functions for five patients with early-stage NPC. Three different planning tumor volumes (PTVs; PTV<sub>1</sub>, PTV<sub>2</sub>, and PTV<sub>3</sub>) were delineated for each patient, and the prescribed doses were 50 Gy, 60 Gy, and 70 Gy (2 Gy/fraction), respectively, for the SEQ technique and 52.8 Gy, 59.4 Gy, and 69.3 Gy (33 fractions), respectively, for the SIB technique.

**Results:** All plans were clinically acceptable. There was no difference in most OED-based SCRs between IMRT and VMAT when the same fractionation scheme was used. Compared with the SEQ technique, the SIB technique in IMRT and VMAT was associated with the lowest OEDs for the oral cavity, pharynx, parotids, and submandibular glands, resulting in SCR reduction. SCR for the parotids was much lower than that for the other assessed organs when the SIB technique was used.

**Conclusion:** Our findings suggest that OED-based SCRs are lower with the SIB technique than with the SEQ technique in IMRT and VMAT in most organs for which SCR was calculated; furthermore, SCR for the parotids is much lower than that for other organs when the SIB technique is used in patients with NPC.

**Keywords:** excess absolute risk, intensity-modulated radiotherapy, organ equivalent dose, secondary cancer risk, volumetric-modulated arc therapy

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## Introduction

Nasopharyngeal carcinoma (NPC) is a rare malignancy in most parts of the world. According to the latest statistics, approximately 80% of patients with NPC are observed in Asia, particularly in Southeast Asia and South China. A previous report

mentioned that the estimated incidence rate of NPC in China was 60.6 per 100,000 individuals and the associated mortality rate was 34.1 per 100,000 individuals.<sup>1</sup>

Radiotherapy (RT) is an essential component of curative-intent treatment for NPC, and stage I disease is treated with RT alone.<sup>2,3</sup> The anatomical locations and proximities of numerous organs at risk (OARs) make RT for NPC very demanding. Different RT modalities, such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT), have been used widely to improve the local control rate of NPC.<sup>4</sup> IMRT can provide better parotid sparing and improved quality of life compared with three-dimensional conformal radiotherapy (3D-CRT) in patients with early-stage NPC.<sup>5,6</sup> IMRT can be applied using either a sequential (SEQ) boost<sup>7,8</sup> or simultaneous integrated boost (SIB) technique.<sup>9,10</sup> Normally, SEQ uses a conventional dose of 1.8–2 Gy/fraction throughout the course of RT, whereas SIB provides an opportunity to simultaneously treat both the primary and secondary targets at different doses.<sup>11</sup>

Although IMRT and VMAT have been shown to improve dose conformity and reduce doses to OARs, low-dose volumes in non-target tissues have been found to be greater with IMRT or VMAT than with 3D-CRT. Radiation exposure of a large volume of non-target tissue might have a negative impact in terms of secondary cancer risk (SCR).<sup>12,13</sup> The exact mechanism of radiation-induced second malignancy is unknown. However, currently, it is a growing concern in oncology because of the high number of cancer survivors, and efforts are being made to prevent or decrease the incidence of radiation-induced second malignancy. Several models exist for the theoretical determination of the risk associated with RT. These models have various degrees of complexity, and they could be used for extrapolating the epidemiological knowledge derived from conventional treatment techniques to new RT techniques and for comparing the risks associated with different treatment techniques.

To our knowledge, only one previous report has compared radiation-induced SCR between IMRT-SIB and VMAT-SIB in patients with NPC<sup>14</sup> and no previous report has compared the SEQ and SIB techniques. The present study aimed to compare SCR, which is considered as a late toxicity, between the SEQ and SIB techniques in IMRT and VMAT in patients with NPC using the concepts of organ equivalent dose (OED) and excess absolute risk (EAR) for dose–response modeling.

## Materials and Methods

### Patient Characteristics

Computed tomography (CT) scans of five patients with NPC who had undergone RT were retrospectively selected for this study. The median age of the patients was 45 years (range, 35–61 years). According to the American Joint Committee on Cancer staging system, the clinical stage distribution of the patients was stage I–II.

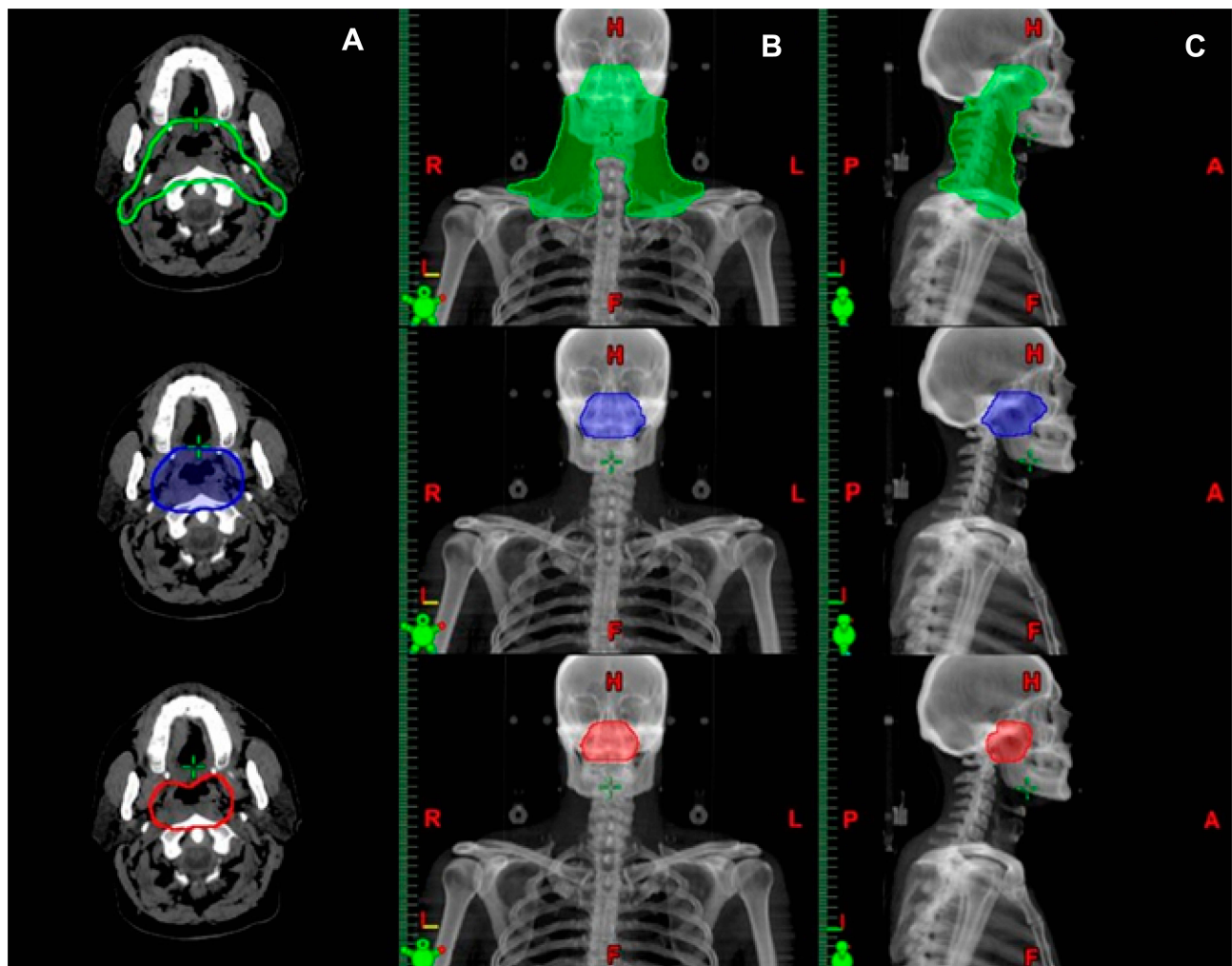
### Ethics Statement

This study was approved by the Karadeniz Technical University, Faculty of Medicine, Farabi Hospital Ethics/Institutional Review Board (Number:2019/264, Date:16.09.2019); due to the secondary use of existing data, the patient informed consent was waived by the institutional review board. All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration.

### Delineation of Target Volumes and Organs at Risk

The patients underwent CT (3-mm slice thickness) in the supine position. Gross tumor volume (GTV) was defined as the visualization of any gross tumor on CT images or other images (magnetic resonance imaging and positron emission tomography). Clinical target volume (CTV) was defined as GTV plus areas considered at risk for containing microscopic disease delineated by a physician. CTV<sub>3</sub> was defined as GTV plus a 5-mm margin around GTV. This margin can be reduced to as low as 1 mm for tumors in close proximity to critical structures. For CTV<sub>2</sub>, all potential routes of spread for primary and nodal GTVs were delineated by a radiation oncologist. For CTV<sub>1</sub>, all levels of the neck, except for level I, were defined as low-risk subclinical regions, with a prescription dose of 50 Gy or 52.8 Gy. A 3-mm margin was added to all CTVs to create respective planning target volumes (PTVs; PTV<sub>1</sub>, PTV<sub>2</sub>, and PTV<sub>3</sub>). The mean PTV<sub>1</sub>, PTV<sub>2</sub>, and PTV<sub>3</sub> volumes of 5 patients were 602 ± 76 cm<sup>3</sup> (range 530–682), 177 ± 7 cm<sup>3</sup> (range 169–184), and 123 ± 27 cm<sup>3</sup> (range 88–147), respectively. PTVs were trimmed to 3 mm from the skin surface (Figure 1).

OARs were delineated according to the Radiation Therapy Oncology Group 0225 protocol.<sup>15</sup> The delineated OARs included the brain stem, spinal cord, oral cavity, pharynx, parotids, submandibular glands, mandible, optic



**Figure 1** Examples of the contours of the planning target volumes (PTVs) in the axial (A), coronal (B), and sagittal (C) planes for a selected patient. Green indicates PTV<sub>1</sub>, blue indicates PTV<sub>2</sub>, and red indicates PTV<sub>3</sub>.

nerves, optic chiasm, lens, mandible, pituitary gland, and soft tissue (total exposed volume minus PTV<sub>1</sub>).

## Treatment Planning

For each patient, IMRT-SEQ, VMAT-SEQ, IMRT-SIB, and VMAT-SIB plans were created with the same goals and objectives. The Eclipse treatment planning system (version 10, Varian Medical Systems, Palo Alto, CA, USA) was used for treatment planning, utilizing 6 MV photon beams.

The SEQ technique had the following three plans: 2 Gy  $\times$  25 fractions (50 Gy) to the low-risk PTV (PTV<sub>1</sub>), followed by two different sequential boosts (2 Gy  $\times$  5 fractions; 60 Gy and 70 Gy) to the medium- and high-risk PTVs (PTV<sub>2</sub> and PTV<sub>3</sub>). On the other hand, the SIB technique involved the treatment of the low-, medium-, and high-risk PTVs with doses of 52.8 Gy, 59.4 Gy, and

69.3 Gy, respectively, in 33 fractions with plan normalization to cover at least 95% of PTV<sub>1</sub> with 95% of the prescribed dose.

SCR was calculated at the brain stem, spinal cord, oral cavity, pharynx, parotids, submandibular glands, mandible, and soft tissue. Dose constraints were used to create acceptable dose limits for the brain stem, spinal cord, and parotids among the organs for which SCR was calculated; the dose constraint process was excluded for other organs, such as the oral cavity, pharynx, submandibular glands, mandible, and soft tissue. The plans were iteratively optimized to obtain optimal coverage of PTVs and sparing of OARs. The dose constraints for the OARs are presented in Table 1.

The IMRT plans involved nine (PTV<sub>1</sub>), seven (PTV<sub>2</sub>), and five (PTV<sub>3</sub>) coplanar fields with equally spaced gantry angles for SEQ and nine coplanar fields with equally

**Table 1** Dose Constraints of the Organs at Risk (OARs)

| OAR             | Goal or Constraint Dose                     |
|-----------------|---|
| Brain stem      | $D_{max} < 54$ Gy                           |
| Spinal cord     | $D_{max} < 46$ Gy                           |
| Parotids        | $D_{mean} \leq 26$ Gy<br>$V_{30} \leq 50\%$ |
| Optic nerves    | $D_{max} < 54$ Gy                           |
| Optic chiasm    | $D_{max} < 54$ Gy                           |
| Pituitary gland | $D_{max} < 54$ Gy                           |
| Lens            | $D_{max} < 25$ Gy                           |

spaced gantry angles for SIB. The VMAT plans involved two full coplanar arcs.

### Calculation of Secondary Cancer Risk Estimates

It is known that for doses below 2 Gy, the dose–response relationship is linear.<sup>12</sup> However, for higher doses and inhomogeneous dose distributions, the dose–response relationship is not linear<sup>12,16</sup> and other dose–response functions are required to describe the relation. To facilitate the estimation of SCR for irradiated organs, Schneider et al introduced the concept of OED, according to which any two dose distributions in an organ are equivalent if they cause the same radiation-induced cancer incidence.<sup>16</sup>

Different models for OED calculation are available according to the different assumptions of cell behavior after dose exposure.<sup>17,18</sup> Schneider’s full mechanistic dose–response model was used in this study. The full mechanistic model accounts for killing and fractionation effects.<sup>18,19</sup> OEDs for the brain stem, spinal cord, oral cavity, pharynx, parotids, and submandibular glands were calculated using a full mechanistic dose–response model based on differential dose–volume histograms (dDVHs), according to the following formula:

$$OED_{mechanistic} = \frac{1}{V_T} \sum_i V_{Di} \frac{e^{-\alpha' D_i}}{\alpha' R} \left( 1 - 2R + R^2 e^{\alpha' D_i} - (1 - R)^2 e^{-\frac{\alpha' R}{1-R} \alpha' D_i} \right)$$

where  $V_T$  is the total organ volume and  $V_{Di}$  is the volume of the organ that is exposed to dose  $D_i$ . The sum involves all the bins of the dose–volume histogram. Additionally, the parameter R describes repopulation and the repair ability between the delivered dose fractions. The parameter  $\alpha'$  is calculated as follows:

$$\alpha' = \alpha + \beta \frac{D}{D_T} d_T$$

where  $\alpha$  and  $\beta$  are parameters from the linear quadratic model of cell killing, describing the linear and quadratic dose response of the tissue to radiation.

OEDs for the mandible and soft tissue were calculated using a specific mechanistic sarcoma model based on intermediate repopulation ( $R = 0.5$ ) according to the following formula:

$$OED_{sarcoma} = \frac{1}{V_T} \sum_i V_{Di} \frac{e^{-\alpha' D_i}}{\alpha' R} \left( 1 - 2R + R^2 e^{\alpha' D_i} - \alpha' R D_i - (1 - R)^2 e^{-\frac{\alpha' R}{1-R} \alpha' D_i} \right)$$

The risk of developing secondary solid cancer after RT is usually represented by EAR. The EAR for the development of solid cancer describes the absolute difference in cancer rates between persons exposed to a dose d and those not exposed to a dose beyond the natural dose exposition per 10,000 persons per year.<sup>18</sup> EAR can be calculated as follows:<sup>18</sup>

$$EAR = EAR_0 \cdot OED \cdot \mu(\text{agex}, \text{agea})$$

where  $EAR_0$  is the initial slope of the dose–response curve at a low dose. The function  $\mu$  takes into account the age of the population examined based on the patient’s age at the time of irradiation (agex) and the attained age of the patient in years (agea). It can be calculated as follows:

$$\mu(\text{agex}, \text{agea}) = \exp[\gamma_e \cdot (\text{agex} - 30) + \gamma_a \cdot \ln(\text{agea}/70)]$$

where  $\gamma_e$  and  $\gamma_a$  are age-modifying factors ( $EAR_0$  was originally calculated for persons exposed at the age of 30 years and attaining the age of 70 years). All EARs in this study were calculated with age modification for patients irradiated at the age of 45 years (agex) and attaining the age of 70 years (agea).

The site-specific parameters were derived from a combined fit to data from atomic bomb survivors and patients treated with RT for Hodgkin disease, assuming an  $\alpha/\beta$  value of 3 Gy.<sup>18</sup> The difference in the baseline risks for developing cancer without exposure to radiation between the Japanese and Western populations was included. The parameters used for the OED and EAR calculations are presented in Table 2.

### Statistical Analysis

The two-tailed Wilcoxon signed-rank test was used to compare differences between the DVH parameters of the IMRT and VMAT plans (each pair of patient-specific DVH

**Table 2** Risk Parameters for All Tissues

| Tissues                           | $\dot{\alpha}$<br>(Gy <sup>-1</sup> ) | R    | EAR <sub>0</sub> | $\gamma_e$ | $\gamma_a$ |
|-----------------------------------|---------------------------------------|------|------------------|------------|------------|
| Brain stem and spinal cord        | 0.018                                 | 0.93 | 0.7              | -0.024     | 2.38       |
| Oral cavity and pharynx           | 0.043                                 | 0.97 | 0.73             | -0.024     | 2.38       |
| Parotids and submandibular glands | 0.087                                 | 0.23 | 0.73             | -0.024     | 2.38       |
| Mandible                          | 0.067                                 | 0.50 | 0.20             | -0.013     | -0.56      |
| Soft Tissue                       | 0.060                                 | 0.50 | 0.60             | -0.013     | -0.56      |

values was compared). All statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). Significance level was set at  $p = 0.05$ .

## Results

The mean volume of the PTV<sub>1</sub>, PTV<sub>2</sub>, and PTV<sub>3</sub> were  $624.96 \pm 112.17 \text{ cm}^3$ ,  $177.58 \pm 6.96 \text{ cm}^3$ , and  $123.44 \pm 27.49 \text{ cm}^3$ , respectively. In all five cases, all plans were clinically acceptable, with at least 95% of the PTVs receiving 95% of the prescribed dose.

The mean parotid volume was  $47 \pm 13.28 \text{ cm}^3$ . For IMRT-SEQ, VMAT-SEQ, IMRT-SIB, and VMAT-SIB, the mean doses ( $D_{\text{mean}}$ ) for the right parotid were  $25.80 \pm 1.83 \text{ Gy}$ ,  $23.23 \pm 0.90 \text{ Gy}$ ,  $25.15 \pm 1.03 \text{ Gy}$ , and  $22.39 \pm 1.23 \text{ Gy}$ , respectively, and those for the left parotid were  $26.70 \pm 1.44 \text{ Gy}$ ,  $23.43 \pm 1.49 \text{ Gy}$ ,  $26.47 \pm 1.19 \text{ Gy}$ , and  $23.31 \pm 0.74 \text{ Gy}$ , respectively. The dosimetric data for the parotids and soft tissue are summarized in Table 3. The  $D_{\text{mean}}$  of the parotids was significantly higher with IMRT than with VMAT for both the SEQ and SIB techniques. The  $V_{30}$  of

the parotids and the soft tissue doses ( $V_1$ ,  $V_3$ , and  $V_5$ ) were not significantly different (Table 3).

The OED and EAR values for all OARs according to the SEQ and SIB techniques in IMRT and VMAT are shown in Table 4. The relative difference between SCRs associated with the SEQ and SIB techniques was greatest for the parotids compared with the findings for all other organs in both IMRT and VMAT, with a reduction of approximately 40% (Table 4). On comparing only the SEQ and SIB techniques, IMRT and VMAT showed similar SCRs (except for the mandible [SEQ] and parotids [SIB]). SIB in both IMRT and VMAT resulted in the lowest OEDs for the oral cavity, pharynx, parotids, and submandibular glands, and was thus associated with SCR reduction compared with SEQ; conversely, SEQ in both IMRT and VMAT significantly reduced the OED and EAR of the soft tissue compared with SIB.

Figure 2 shows the OED and EAR values for all OARs stratified according to the techniques. As shown in Figure 2E, the EAR-SEQ:EAR-SIB ratio was the greatest for the parotids compared with the findings for all other OARs, indicating that parotids have a higher SCR with the SEQ technique than with the SIB technique.

## Discussion

Owing to technological advancements, new RT techniques, such as IMRT, have been developed with the intention of not only improving tumor coverage but also sparing OARs compared with traditional two-dimensional RT.<sup>5,20-22</sup> Furthermore, VMAT has been shown to be superior to IMRT with regard to improving dose homogeneity and sparing critical organs at multiple tumor sites.<sup>23-25</sup>

**Table 3** Comparison of the Parotid and Soft Tissue Dose–Volume Metrics as a Function of Plan Modality

| Metric                 | IMRT-SEQ         | VMAT-SEQ         | IMRT-SIB         | VMAT-SIB         | IMRT-SEQ vs VMAT-SEQ p-value | IMRT-SIB vs VMAT-SIB p-value | IMRT-SEQ vs IMRT-SIB p-value | VMAT-SEQ vs VMAT-SIB p-value |
|------------------------|------------------|------------------|------------------|------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| <b>Right parotid</b>   |                  |                  |                  |                  |                              |                              |                              |                              |
| $D_{\text{mean}}$ (Gy) | $25.80 \pm 1.83$ | $23.23 \pm 0.90$ | $24.85 \pm 1.03$ | $22.39 \pm 1.23$ | <b>0.045</b>                 | <b>0.014</b>                 | 0.557                        | 0.310                        |
| $V_{30}$ (%)           | $24.25 \pm 3.78$ | $19.75 \pm 1.71$ | $22.00 \pm 2.45$ | $18.25 \pm 2.06$ | 0.093                        | 0.058                        | 0.362                        | 0.305                        |
| <b>Left parotid</b>    |                  |                  |                  |                  |                              |                              |                              |                              |
| $D_{\text{mean}}$ (Gy) | $26.70 \pm 1.44$ | $23.43 \pm 1.49$ | $25.87 \pm 1.19$ | $22.85 \pm 0.74$ | <b>0.020</b>                 | <b>0.004</b>                 | 0.810                        | 0.892                        |
| $V_{30}$ (%)           | $25.75 \pm 4.35$ | $24.00 \pm 3.92$ | $24.25 \pm 4.65$ | $21.25 \pm 2.63$ | 0.572                        | 0.304                        | 0.654                        | 0.288                        |
| <b>Soft tissue</b>     |                  |                  |                  |                  |                              |                              |                              |                              |
| $V_1$ (%)              | $98.65 \pm 1.16$ | $99.9 \pm 0.00$  | $98.73 \pm 1.09$ | $99.9 \pm 0.00$  | 0.121                        | 0.119                        | 0.928                        | 0.724                        |
| $V_3$ (%)              | $96.63 \pm 1.04$ | $97.45 \pm 0.50$ | $96.75 \pm 1.16$ | $97.53 \pm 0.42$ | 0.203                        | 0.256                        | 0.878                        | 0.826                        |
| $V_5$ (%)              | $91.28 \pm 1.94$ | $93.30 \pm 0.63$ | $92.35 \pm 1.66$ | $94.05 \pm 0.95$ | 0.094                        | 0.126                        | 0.432                        | 0.236                        |

**Notes:** The bold values indicate significant differences.

**Abbreviations:** IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; SEQ, sequential boost; SIB, simultaneous integrated boost;  $D_{\text{mean}}$ , mean dose;  $V_x$ , volume (%) receiving x dose (Gy) or higher; Gy, Gray.

**Table 4** OED and EAR Values for All OARs According to the SEQ and SIB Techniques in IMRT and VMAT

| Sites               | Model            | IMRT-SEQ     | VMAT-SEQ     | IMRT-SIB     | VMAT-SIB     | IMRT-SEQ vs VMAT-SEQ p-value | IMRT-SIB vs VMAT-SIB p-value | IMRT-SEQ vs IMRT-SIB p-value | VMAT-SEQ vs VMAT-SIB p-value |
|---------------------|------------------|--------------|--------------|--------------|--------------|------------------------------|------------------------------|------------------------------|------------------------------|
| Brain stem          | OED <sup>a</sup> | 19.27 ± 1.94 | 18.99 ± 1.04 | 19.68 ± 1.62 | 21.43 ± 2.25 | 0.291                        | 0.094                        | 0.254                        | 0.097                        |
|                     | EAR <sup>b</sup> | 7.78 ± 0.79  | 7.71 ± 0.42  | 7.92 ± 0.66  | 8.70 ± 0.92  | 0.295                        | 0.095                        | 0.255                        | 0.098                        |
| Spinal cord         | OED <sup>a</sup> | 14.34 ± 2.28 | 13.36 ± 1.23 | 15.29 ± 2.34 | 16.36 ± 1.52 | 0.479                        | 0.470                        | 0.583                        | <b>0.022</b>                 |
|                     | EAR <sup>b</sup> | 5.82 ± 0.93  | 5.43 ± 0.50  | 6.21 ± 0.95  | 6.65 ± 0.62  | 0.481                        | 0.469                        | 0.581                        | <b>0.022</b>                 |
| Oral cavity         | OED <sup>a</sup> | 18.80 ± 0.78 | 19.03 ± 0.87 | 17.48 ± 0.42 | 17.27 ± 0.41 | 0.715                        | 0.490                        | <b>0.025</b>                 | <b>0.011</b>                 |
|                     | EAR <sup>b</sup> | 7.96 ± 0.33  | 8.06 ± 0.37  | 7.40 ± 0.18  | 7.31 ± 0.17  | 0.715                        | 0.505                        | <b>0.025</b>                 | <b>0.010</b>                 |
| Pharynx             | OED <sup>a</sup> | 24.62 ± 2.05 | 24.57 ± 2.30 | 20.39 ± 0.33 | 20.25 ± 0.35 | 0.975                        | 0.583                        | <b>0.024</b>                 | <b>0.031</b>                 |
|                     | EAR <sup>b</sup> | 10.43 ± 0.87 | 10.40 ± 0.98 | 8.63 ± 0.14  | 8.58 ± 0.15  | 0.974                        | 0.595                        | <b>0.024</b>                 | <b>0.032</b>                 |
| Parotids            | OED <sup>a</sup> | 6.63 ± 0.89  | 6.73 ± 0.63  | 3.96 ± 0.04  | 4.06 ± 0.06  | 0.860                        | <b>0.030</b>                 | <b>0.009</b>                 | <b>&lt;0.001</b>             |
|                     | EAR <sup>b</sup> | 2.81 ± 0.38  | 2.85 ± 0.27  | 1.68 ± 0.02  | 1.72 ± 0.03  | 0.859                        | <b>0.038</b>                 | <b>0.009</b>                 | <b>&lt;0.001</b>             |
| Submandibular gland | OED <sup>a</sup> | 3.30 ± 0.18  | 3.67 ± 0.27  | 2.95 ± 0.09  | 3.07 ± 0.14  | 0.062                        | 0.222                        | <b>0.014</b>                 | <b>0.007</b>                 |
|                     | EAR <sup>b</sup> | 1.40 ± 0.07  | 1.55 ± 0.11  | 1.25 ± 0.04  | 1.30 ± 0.06  | 0.059                        | 0.239                        | <b>0.012</b>                 | <b>0.007</b>                 |
| Mandible            | OED <sup>a</sup> | 3.85 ± 0.81  | 2.62 ± 0.29  | 3.87 ± 0.32  | 3.33 ± 0.33  | <b>0.027</b>                 | 0.054                        | 0.991                        | <b>0.017</b>                 |
|                     | EAR <sup>b</sup> | 0.66 ± 0.14  | 0.45 ± 0.05  | 0.67 ± 0.05  | 0.57 ± 0.06  | <b>0.047</b>                 | 0.057                        | 0.998                        | <b>0.020</b>                 |
| Soft tissue         | OED <sup>a</sup> | 2.25 ± 0.10  | 2.07 ± 0.15  | 2.74 ± 0.11  | 2.58 ± 0.17  | 0.095                        | 0.174                        | <b>0.001</b>                 | <b>0.004</b>                 |
|                     | EAR <sup>b</sup> | 1.16 ± 0.05  | 1.07 ± 0.08  | 1.41 ± 0.06  | 1.33 ± 0.09  | 0.086                        | 0.169                        | <b>0.001</b>                 | <b>0.004</b>                 |

**Notes:** The means and standard deviations of the OED and EAR values for all patients are presented. The bold values indicate significant differences. <sup>a</sup>Unit is Gray, <sup>b</sup>Unit is per 10,000 persons per year.

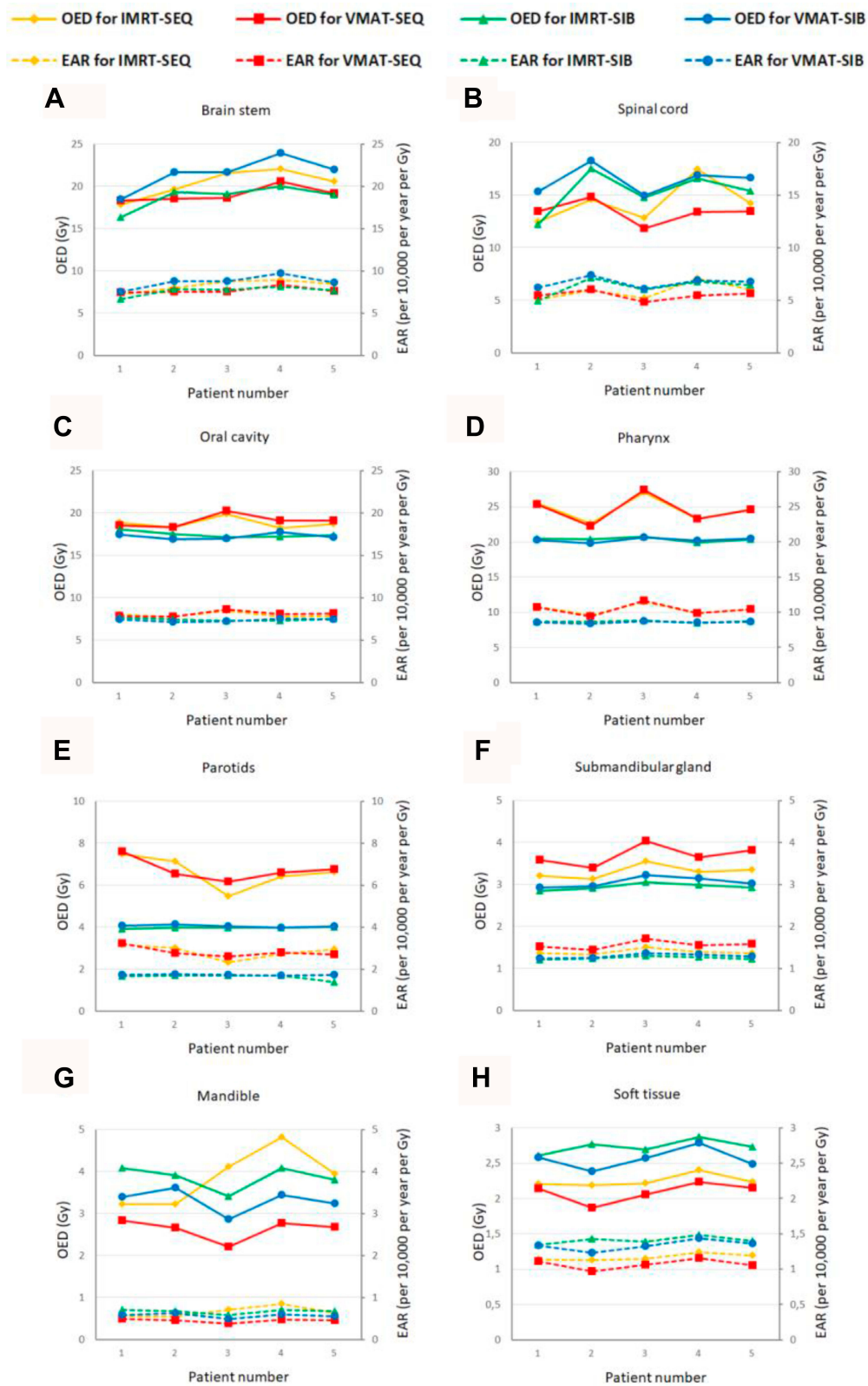
**Abbreviations:** OED, organ equivalent dose; EAR, excess absolute risk; OARs, organs at risk; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; SEQ, sequential boost; SIB, simultaneous integrated boost.

IMRT and VMAT can be applied using either the SEQ or SIB technique. The SIB technique allows simultaneous delivery of different doses to different target volumes within a single treatment fraction, enabling the shortening of treatment duration and enhancing the biological equivalent dose. Most clinical studies involving NPC used the SIB technique<sup>9,10,22,26</sup> and rarely performed comparisons with the other technique.<sup>7,8,27</sup> To our knowledge, only one previous study has compared the radiation-induced SCR between IMRT-SIB and VMAT-SIB in patients with NPC<sup>14</sup> and no previous report has compared the SEQ and SIB techniques in terms of SCR. Therefore, the findings of the present study comparing the SEQ and SIB techniques in IMRT and VMAT are important.

Dosimetric studies comparing IMRT-SEQ and IMRT-SIB revealed that both techniques provided the same target coverage; however, IMRT-SIB showed better parotid sparing, whereas IMRT-SEQ lowered the maximum doses to the spinal cord and brain stem.<sup>28,29</sup> In the present study, all plans showed equally good PTV coverage. Our dosimetric data indicated that parotid sparing was slightly better with IMRT-SIB and VMAT-SIB than with IMRT-SEQ and VMAT-SEQ in terms of the  $D_{mean}$  and  $V_{30}$ ; however,

there were no significant differences. According to our results, the  $D_{mean}$  to the parotids was significantly lower in VMAT than in IMRT for both SEQ and SIB.

In this study, most OED-based SCRs, including those in the oral cavity, pharynx, parotids, and submandibular glands, were significantly lower with the IMRT-SIB and VMAT-SIB plans than with the IMRT-SEQ and VMAT-SEQ plans. However, the most striking result in our study was regarding SCR for the parotids. The relative difference in SCR between the SEQ and SIB techniques was the greatest for the parotids in both IMRT and VMAT, with an approximately 40% reduction with the SIB technique, although there were no significant differences with regard to the  $D_{mean}$  and  $V_{30}$  of the parotids. In this study, SCR was calculated on the basis of the radiation dose received by OARs. To calculate the risks of nonhomogeneous doses to the organs, the concept of OED was used for directly considering the dose–response relationship for the organs. Our results showed that although there was no difference between the plans in terms of  $D_{mean}$ , there could be a difference in terms of SCR associated with  $D_{max}$  and nonhomogeneous dose distribution in the organs. In NPC cases, the parotids might touch the treatment field



**Figure 2** Graphs showing correlations between organ equivalent doses (OEDs) and excess absolute risks (EARs) for all organs at risk (OARs) stratified by four plans. (A) Brain stem, (B) spinal cord, (C) oral cavity, (D) pharynx, (E) parotids, (F) submandibular glands, (G) mandible, and (H) soft tissue.

**Abbreviations:** IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; SEQ, sequential boost; SIB, simultaneous integrated boost.

(especially with regard to PTV<sub>1</sub>), and we should pay particular attention to the organs near a treated region considering the secondary malignancy potential.

In a study by Lee et al differences in SCR between IMRT-SIB and VMAT-SIB were assessed with regard to NPC. The authors found that the OED-based SCR was slightly higher for the oral cavity and mandible when VMAT-SIB was used.<sup>14</sup> According to their results, there was no significant difference in terms of SCR to other organs, including the brain stem, parotids, pharynx, submandibular glands, lungs, spinal cord, and healthy tissue. The present study found no differences between IMRT-SIB and VMAT-SIB for the oral cavity and mandible and found that SCR was slightly higher for the parotids when VMAT-SIB was used. A direct comparison of our data with data from other groups is not straightforward because of the possible differences in GTV delineation, treatment margins, irradiation volume, and adopted methods.

VMAT was equivalent or superior to IMRT in terms of PTV coverage and OAR sparing. However, higher SCR should be taken into consideration; it might be caused by the distribution of low-dose radiation to non-target healthy tissue.<sup>14,30</sup> According to our results, there were no significant differences between IMRT and VMAT regarding V<sub>1</sub>, V<sub>3</sub>, and V<sub>5</sub> values with both the SEQ and SIB techniques and regarding SCR with the same techniques for the soft tissue. However, SCR for the soft tissue was significantly lower with the SEQ technique than with the SIB technique in both IMRT and VMAT.

There are a number of limitations in our work. We performed this analysis of the SCR in only five patients. Other studies involving similar cancer risk assessments also used a small number of patients (typically two to three cases per study). The reason for the relatively small sample size in this type of studies is that the primary interest is the investigation of the differences between planning techniques rather than the factors associated with inter-patient variability.<sup>31,32</sup> There are also other uncertainties in radiation-induced secondary cancer models and parameters.

In epidemiological studies, radiation-induced malignancy might be influenced by factors such as radiation dose and age at initial exposure.<sup>33</sup> In this study, the median age of the patients was 45 years (range, 35–61 years). We selected patients who were relatively young at the time of treatment to take into account the age dependence of SCR. All SCRs were calculated with age modification for patients irradiated at the age of 45 years (because the

median age of the patients is 45 years) and attaining the age of 70 years to obtain exact SCRs. SCR is a non-negligible late complication encountered by young patients, especially long-term survivors of NPC.

In this study, most OED-based SCRs were significantly lower with the SIB technique than with the SEQ technique. However, SIB might carry a high risk of regional recurrence because of the low dose per fraction at the elective nodal region and might cause late adverse toxicities because of the high dose per fraction near GTV. For further clarification, randomized clinical trials comparing the treatment outcomes between these two techniques are needed.

## Conclusion

IMRT and VMAT are the standards of care for NPC and can be applied using either the SEQ or SIB technique. Although IMRT and VMAT have become common treatment modalities for NPC, there is concern regarding SCR associated with their use. Our findings suggest that OED-based SCRs are usually lower with the SIB technique than with the SEQ technique in IMRT and VMAT and that SCR for the parotids is dramatically lower than that for other organs when the SIB technique is used in patients with NPC.

## Disclosure

The authors report no conflicts of interest in this work.

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