Survival outcomes and failure patterns for oropharyngeal cancers treated with simultaneous integrated boost in intensity modulated radiotherapy (SIB-IMRT) and concurrent chemotherapy

Výsledky přežití a vzorce selhání léčby u orofaryngeálních karcinomů léčených radioterapií s modulovanou intenzitou svazku se simultánním integrovaným boostem (SIB-IMRT) a souběžnou chemoterapií

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Summary

Background: Intensity modulated radiotherapy (IMRT) has become a standard radiotherapy treatment delivery option owing to the advantages it offers in terms of target coverage and organ sparing. Furthermore, the ability to introduce different fractionation for different targets lets us deliver higher doses to the high-risk areas and lower doses to the elective volumes at the same sitting, referred to as simultaneous integrated boost (SIB). In the current study, we intended to retrospectively analyze the clinical outcomes and patterns of the failure of oropharyngeal cancers treated with SIB-IMRT and concurrent chemotherapy at our centre and analyze the factors contributing to poorer outcomes. ***Material and methods:*** Data of oropharyngeal cancer patients treated with SIB-IMRT and concurrent chemotherapy were retrieved from the institutional database. Patient demographic details, histopathological features, staging, treatment details, failure patterns and outcomes were documented. All potential factors were evaluated for outcomes. Radiation was delivered by using the SIB-IMRT technique. High-risk planning target volume (PTV) received 66 Gy in 2.2 Gy/fraction, intermediate and low-risk PTV received 60 Gy and 54 Gy, respectively. Primary endpoint was to assess local control (LC), regional control (RC) and loco-regional control (LRC) rates and secondary end point was to evaluate the survival outcomes – overall survival (OS) and cancer-specific mortality. All survival analyzes were performed using the Kaplan-Meier method. ***Results:*** A total of 169 cases were included in the final analysis. The median age was 55 years (range 20–78) with 95.3% males. The base of tongue was the most common primary site. Around 54% cases were node negative with 38% patients having stage IV disease. The local control rates for N0 vs. N+ cases were 74.1 vs. 62.3% (P = 0.046), respectively. Similarly, the 4-year RC rates for N0 vs. N+ cases were 94.4 vs. 83.5% (P = 0.024), respectively. On multivariate analysis, only 4-year RC rates showed significant difference between the two (P = 0.039). No differences were found between T stages in LRC and OS. The 4-year LRC rates for stages 1, 2 vs. 3, 4 were non-significant (69.2 vs. 66.3%; P = 0.178). The 4-year OS rate was 81.3%. The 4-year LC and LRC rates were 67.8 and 89.5%, respectively. There were 54 local and 17 regional failures. The median time to failure was 13 months (range 3.6–82.9). ***Conclusion:*** SIB-IMRT provides comparable outcomes for oropharyngeal cancers. OS and loco-regional recurrences were significantly worse for nodal positive disease.

Key words

IMRT – SIB-IMRT – local control rate – node positive – regional control rate

The authors declare that they have no potential conflicts of interest concerning drugs, products, or services used in the study.

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Souhrn

Východiska: Radioterapie s modulovanou intenzitou svazku (intensity modulated radiotherapy – IMRT) stala v radioterapii standardem díky výhodám, které poskytuje z hlediska pokrytí cílových objemů a šetrnosti vůči orgánům. Možnost frakcionace dávek pro různé cíle navíc umožňuje ozařovat v rámci stejného sezení vysoce rizikové oblasti vyššími dávkami a volitelné objemy nižšími dávkami, což se označuje jako simultánní integrovaný boost (SIB). Cílem této studie byla retrospektivní analýza klinických výsledků a vzorců selhání léčby u pacientů, kteří byli v našem centru léčeni pro karcinomy orofaryngu pomocí SIB-IMRT a souběžné chemoterapie a zároveň analýza faktorů přispívajících k horším výsledkům. ***Materiál a metody:*** Údaje o pacientech s karcinomem orofaryngu léčených pomocí SIB-IMRT a souběžné chemoterapie byly získány z nemocniční databáze. Byly zdokumentovány demografické údaje pacientů, histopatologické znaky, staging, podrobnosti o léčbě, vzorce selhání léčby a výsledky. Byly vyhodnoceny všechny potenciální faktory ovlivňující výsledky. Ozařování probíhalo technikou SIB-IMRT. Celková dávka na plánovací cílový objem (planning target volume – PTV) s vysokým rizikem byla 66 Gy (2,2Gy/frakce), celkové dávky na PTV se středním a nízkým rizikem byly 60 Gy a 54 Gy. Primárním endpointem byla hodnocení míry lokální kontroly (local control – LC), regionální kontroly (RC) a lokoregionální kontroly (LRC) a sekundárním endpointem bylo hodnocení výsledků přežití: celkového přežití (overal survival – OS) a úmrtnost na nádorové onemocnění. Všechny analýzy přežití byly provedeny pomocí Kaplanovy-Meierovy metody. ***Výsledky:*** Do finální analýzy bylo zahrnuto 169 pacientů. Medián věku byl 55 let (rozmezí 20–78) a 95,3 % tvořili muži. Nejčastějším primárním místem výskytu nádoru byla báze jazyka. Celkem 54 % pacientů mělo negativní uzliny a u 38 % bylo onemocnění ve stadiu IV. LC u případů N0 vs. N+ byla 74,1 vs. 62,3 % (p = 0,046). Stejně tak čtyřletá RC pro případy N0 vs. N+ byla 94,4 vs. 83,5 % (p = 0,024). Při multivariační analýze vykazovala signifikantní rozdíl mezi oběma případy pouze čtyřletá RC (p = 0,039). Mezi stadii T nebyly zjištěny žádné rozdíly v LRC a OS. Čtyřletá LRC pro stadia 1 a 2 vs. 3 a 4 byla nevýznamná (69,2 vs. 66,3 %; p = 0,178). Čtyřleté OS bylo 81,3 %. Čtyřletá LC a LRC byla 67,8 a 89,5 %. Bylo zaznamenáno 54 lokálních a 17 regionálních selhání léčby. Medián doby do selhání léčby byl 13 měsíců (rozmezí 3,6– 82,9). ***Závěr:*** SIB-IMRT poskytuje u karcinomů orofaryngu srovnatelné výsledky. Celkové přežití a lokoregionální recidivy byly významně horší u onemocnění s pozitivními uzlinami.

Klíčová slova

IMRT – SIB-IMRT – míra lokální kontroly – pozitivní uzliny – míra regionální kontroly

Introduction

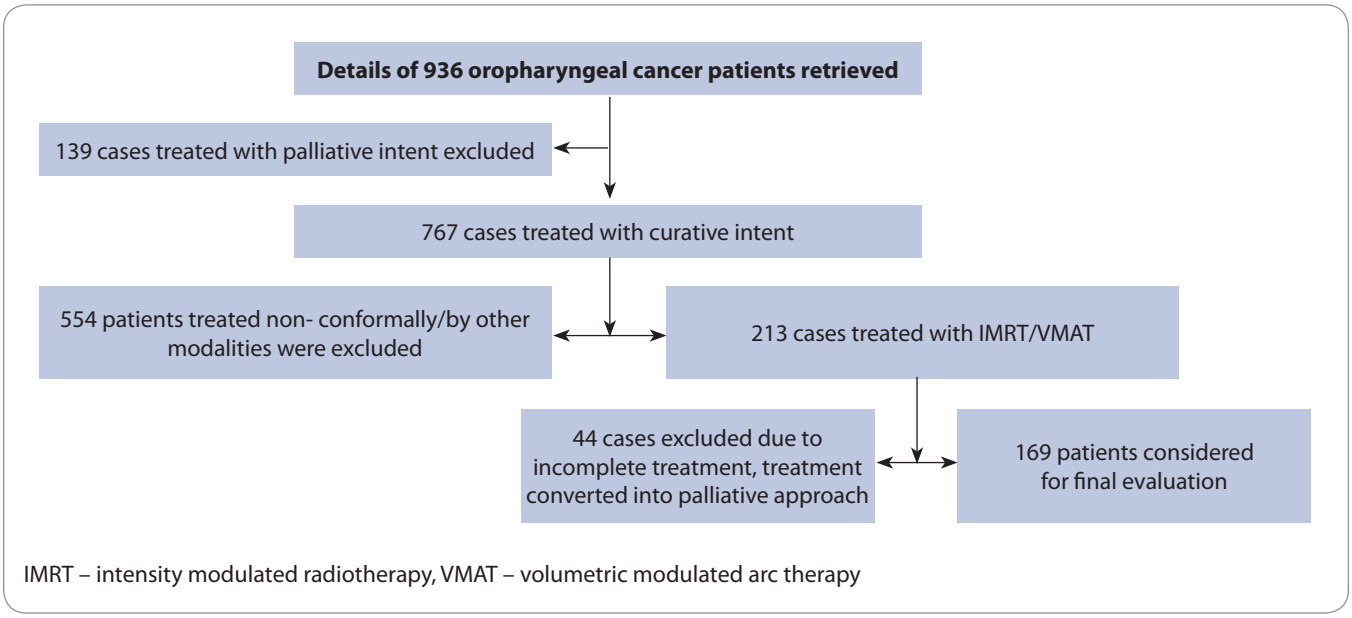
Oropharyngeal cancer (OPC) is one of the most common head and neck cancers accounting for 20,617 new cases per year and 12,703 deaths per year in India [1]. Concurrent chemo-radiotherapy (CHRT) is the established standard of care for these cancers [2]. In the 21st century, intensity modulated radiotherapy (IMRT) has become the standard radiotherapy treatment delivery option owing to the various advantages it offers in terms of target coverage [3,4] and organ sparing [5]. IMRT delivers precise radiation therapy to the intended target volumes with sub-centimetric accuracy depending upon the machines used to deliver irradiation. An additional advantage is reduced dose deposited to the organ at risks (OARs). Reduced dose to parotid glands results in decreased xerostomia rates [5] and decreased spinal cord doses enable us to escalate doses when re-irradiation is indicated in recurrent cancers [6]. Furthermore, the ability to introduce different fractionation for different targets lets us deliver higher doses to the high-risk areas and lower doses to the elective volumes, which is commonly referred to as simultaneous integrated boost (SIB) [7]. This fractionation schedule enables us to counter the radiobiologic effects of tumors like accelerated repopulation as we deliver a higher dose per fraction to the target using lesser number of fractions as compared to the conventional 2 Gy per fraction [8]. In the current study, we intended to retrospectively analyze the clinical outcomes and patterns of failure of oropharyngeal cancers treated with SIB-IMRT and concurrent chemotherapy at our centre and analyze the factors contributing to poorer outcomes.

Material and methods

Between March 2017 and December 2021, oropharyngeal squamous cell carcinoma patients, treated with concurrent CHRT to primary and bilateral cervical nodes, were evaluated for better knowledge about recurrence patterns with IMRT/volumetric arc therapy (VMAT). Institutional review committee approval was taken. The data of 936 oropharyngeal cancer patients were retrieved from the records and electronic database archives of the institute. From this data, 169 cases of oropharyngeal cancers treated with IMRT/VMAT were considered for the final analysis. The consort diagram representing the actual number of patient data retrieved has been mentioned in Scheme 1.

All the records were reviewed for each patient: age, gender, site and extent of tumor, staged as per the 8th edition of the American Joint Committee on Cancer [9], histopathological findings, pretreatment investigations, radiotherapy and chemotherapy modalities used for treatment delivering, time taken for treatment completion, compliance to treatment, follow-ups, local and regional recurrence in ipsilateral and contralateral neck, progression-free survival (PFS) and overall survival (OS). Patients treated by non-conformal approaches are excluded. The patients having tumors in any site other than oropharynx or previously treated head and neck cancers were excluded from the study. Patients with incomplete treatment or treated through a palliative approach were excluded. Due to limited availability regarding the data of human papilloma virus (HPV) for all the patients in our database, we have not included HPV as a parameter in the staging and prognostication of these cancers.

Patients were immobilized using a custom made 4 or 5 clamp head and neck thermoplastic mask, with the head in a neutral position. A 3-mm slice thickness contrast enhanced computed tomography (CT) images were obtained



Scheme 1. Consort diagram representing the patient data retrieved and used for evaluation.

from skull vertex to 2 cm below the carina using Siemens Emotion 6 (Somatom, Germany). The CT data-set was imported to MONACO (Version 5.11) treatment planning systems for contouring and planning.

The target volumes included the primary gross tumor volumes (GTV-P) and involved lymph nodes (GTV-N) as determined by clinical, imaging and endoscopic findings. Different clinical target volumes (CTV), i.e. subclinical regions at risk for involvement were defined as follows.

The high-risk clinical target volume (HR-CTV) included GTV with 5-mm margins. The intermediate-risk volume (IR-CTV) encompassed GTV with 1-cm margins and potential sites of microscopic extension. Low-risk (LR-CTV) included nodal areas at very less chance of subclinical sub-microscopic spread. The volumes were contoured as per delineation guide for oropharynx. To account for organ motion/daily treatment set-up uncertainties, high-risk, intermediate--risk and low-risk planning target volumes (HR-PTV, IR-PTV and LR-PTV) were created (i.e., additional 5-mm margin) to each of the above CTVs, i.e. to HR-CTV, IR-CTV and LR-CTV, respectively.

OARs were contoured: brainstem, spinal cord, parotid glands, eyeball, lens, optic nerves, chiasm, pituitary gland, temporal lobes, mandible and temporomandibular joint. Planning organ at risk volumes (PRV) were created for brainstem, spinal cord and other critical structures using a 3-mm margin. The standard dose constraints to these critical structures were used and all efforts were made to achieve the constraints as close as possible [10].

Radiation was delivered by using a simultaneous integrated boost technique. HR-PTV received 66 Gy in 2.2 Gy/fraction, IR-PTV received 60 Gy in 2 Gy/fraction, and LR-PTV received 54 Gy in 1.8 Gy/fraction over 30 days. All potential sites of local infiltration and bilateral neck received at least 54 Gy/30 fraction which equals to the equivalent dose in 2-Gy fractions (EQD2) of 53.1 Gy.

Radiotherapy was delivered using 6-MV photons, one fraction per day, 5 days per week by using linear accelerator Elekta Synergy (Crowley UK) with a leaf width of 1 cm at isocentre. Patients were treated with IMRT conformal radiotherapy via 7–9 fixed gantry angles with step-and-shoot treatment or with VMAT by two complete arcs 179–181 and 181–179 degree gantry angles as considered apt by medical physicists. The median RT dose delivered was 66 Gy (range 59.4–70.4 Gy). The planning objective was to reduce the spinal cord dose to < 45 Gy while ensuring PTV coverage of $\geq 95\%$.

Patients with advanced stage disease (bulky T2, T3–4, node positive) received concurrent weekly cisplatin 40 mg/m^2 flat dose or concurrent weekly carboplatin according to AUC 2; antiemetic prophylaxis, and adequate hydration as per institution protocol. Neoadjuvant chemotherapy (NACT) was given to decrease the tumor size mainly in patients with stage 3 and 4 in whom up--front definitive concurrent CHRT could not be approached due to the vicinity of the tumor to critical structures and dose constraints could not be achieved by radiotherapy without tumor dose compromise. Two to three cycles of TPF (docetaxel, cisplatin, 5-fluorouracil) or PF (paclitaxel and carboplatin) NACT were given every 21 days.

All patients were followed up on a regular basis: monthly once for the first 6 months, every 2 months for the next year, every 3 months for the third and fourth years, and then 6 months to annually thereafter. Response assessment scans were done after 3 months of treatment completion along with endoscopy and biopsy if mandated. The response assessment scan was primarily MRI for the base of tongue tumors and head neck and thorax contrast enhanced CT for others.

Primary endpoint was to assess local control (LC), regional control (RC) and

Tab. 1. Patient demographics.

Characteristics		N = 169	%
Age	< 50 years	48	28.4
	> 50 years	121	71.6
Gender	male	161	95.3
	female	8	4.7
Site	tonsil	44	26
	base of tongue	83	49.1
	soft palate	35	20.7
	oropharyngeal wall	7	4.1
Differentiation	well dif.	27	16
	moderately dif.	129	76.3
	poorly dif.	13	7.7
T stage	T1	31	18.3
	T2	57	33.7
	T3	23	13.6
	T4a	52	30.8
	T4b	6	3.6
N stage	N0	92	54.4
	N1	62	36.7
	N2a	9	5.3
	N2b	4	2.4
	N2c	2	1.2
AJCC 8th stage	I	22	13
	II	32	18.9
	III	51	30.2
	IV	64	37.9
NACT	no	163	96.4
	yes	6	3.6
Concurrent CHT	no	2	1.2
	yes	167	98.8

AJCC 8th – American Joint Committee on Cancer, Cancer Staging Manual, 8th edition, CHT – chemotherapy, dif. – differentiated, NACT – neo-adjuvant chemotherapy

loco-regional control (LRC) rates and secondary end point was to evaluate the survival outcome: overall survival (OS) and cancer specific mortality (CSM). Locoregional failure was defined as the persistence of tumor in the oropharynx or cervical node metastasis or both after completion of treatment. All time intervals were calculated from the date of diagnosis to the date of the event of interest. OS was measured from the date of diagnosis to the date of death from any cause. CSM was defined as a death due to cancer. Statistical analysis was performed with the SPSS statistical software package for Mac (version 23.0; IBM, Armonk, NY, USA). All survival analyzes were performed using Kaplan-Meier method [11]. The log-rank test was used to test the statistical significance of differences in the survival and control rates for uni-variate analysis. $P < 0.05$ was considered statistically significant. The Cox-regression was used for multi-variate analysis for the variables which were significant in log. All potential prognostic factors were analyzed.

Results

A total of 169 patients were included in the final analysis. The median age was 55 years (range 20–78). Patient demographics are enumerated in Tab. 1. The majority of the cases were base of tongue and tonsillar cancers, accounting for three fourths of the total cases. Sixteen (9.4%) patients received NACT. Most common NACT regimen used was TPF. A total of 93% (155/169) patients received concurrent chemotherapy, 81% (126/155) received concurrent cisplatin and the rest of the patients received concurrent carboplatin. The median concurrent chemotherapy cycles received were 6 (range 2–7). Seventeen patients required granulocyte-colony stimulating factor support. The median RT dose delivered was 66 Gy (range 66–70). Twenty-four cases required feeding tube till one month after RT completion. The median follow-up was 47.5 months (range 6–141.1).

The log-rank analysis showed significant difference between LRC rates for male vs. female ($P = 0.039$), but since the number of females was much lower, further multi-variate analysis was not performed. The 4-year LC and LRC rates were 67.8 and 89.5%, respectively. There were 54 local and 17 regional failures. The median time to failure was 13 months (range 3.6–82.9).

No differences were found in between T stages in LRC and OS. The number of events for different T stages for OS were 4/31, 8/57, 5/23 and 11/58 for T1–T4, respectively. The 4-year OS rates were 86.4, 87.9, 78 and 80%, respectively ($P = 0.615$). No significant difference in OS was found between early and advanced T-stage ($P = 0.231$) (Graph 1). The details have been mentioned in Tab. 2.

Tab. 2. Variation of outcomes with prognostic factors in the univariate analysis.

Variables	P-value				
	LC	RC	LRC	OS	CSM
Gender (male vs. female)	0.039	0.282	0.037	0.459	0.896
Site (tonsil vs. base of tongue vs. soft palate vs. oropharyngeal wall	0.199	0.764	0.210	0.854	0.790
Site (base of tongue vs. others)	0.192	0.419	0.218	0.799	0.625
Age (> 50 vs. < 50 years)	0.106	0.633	0.120	0.677	0.317
Differentiation (well vs. moderately vs. poorly differentiated)	0.211	0.427	0.052	0.180	0.118
T (1 vs. 2 vs. 3 vs. 4)	0.613	0.509	0.636	0.157	0.573
T (1, 2 vs. 3, 4)	0.690	0.353	0.786	0.231	0.469
N (0 vs. 1 vs. 2)	0.244	0.049	0.245	0.643	0.532
N (0 vs. 1, 2)	0.046	0.024	0.048	0.455	0.410
N (0, 1 vs. 2)	0.595	0.108	0.639	0.835	0.615
Stage (1 vs. 2 vs. 3 vs. 4)	0.667	0.254	0.664	0.840	0.734
Stage (1, 2 vs. 3, 4)	0.159	0.169	0.178	0.913	0.622

CSM – cancer specific mortality, LC – local control, LRC – locoregional control, OS – overall survival, RC – regional control

Tab. 3. Multivariate analysis showing relation of node positivity with outcomes.

Variable	LC		RC		LRC		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
N0 vs. N positive	0.582 (0.338–1.005)	0.052	0.334 (0.118–0.948)	0.039	0.586 (0.340–1.010)	0.054	1.409 (0.645–3.078)	0.390
N1,2 vs. N3,4	0818 (0.325– 2.058)	0.669	0.383 (0.110–1.336)	0.132	0.842 (0.335–2.118)	0.715	0.869 (0.205–3.685)	0.849

LC – local control, LRC – locoregional control, RC – regional control

The local control rates for N0 vs. N+ cases were 74.1 vs. 62.3% (P = 0.046), respectively. Similarly, 4-year RC rates for N0 vs. N+ cases were 94.4 vs. 83.5% (P = 0.024), respectively. The LRC rate also showed significant difference with 74.1 vs. 61% (P = 0.048) (Graph 2). OS and CSM did not show significant difference in the univariate analysis. In the multivariate analysis, only 4-year RC rates showed significant difference between the two parameters (P = 0.039; HR 0.334, 95% CI 0.118–0.948) (Graph 3). The details of the multivariate analysis are mentioned in Tab. 3. The univariate analysis for N0, 1 vs. N2, 3 did not yield any significant difference in outcomes in the univariate or multivariate analyses. Nodal staging did not affect overall survival outcomes.

The 4-year LRC rates for stages 1, 2 vs. 3, 4 were non-significant (69.2 vs. 66.3, P = 0.178). The univariate analyses of prognostic factors for other survival outcomes were non-significant. The 4-year OS rates was 81.3%. Among other prognostic factors, analysis for site (the base of tongue vs. tonsil vs. soft palate vs. oropharyngeal wall, the base of tongue vs. other sites and tonsil vs. other sites), differentiation (well differentiated vs. moderately differentiated vs. poorly differentiated and poor differentiation vs. others) and age (< 50 years vs. > 50 years), did not reveal any significant difference for any of the evaluated outcomes.

Discussion

The use of IMRT in OPCs reduces feeding tube dependence and toxicity related outcomes with older techniques like three dimensional conformal radiotherapy (3D-CRT), thereby improving functional outcomes and quality of life [5,12]. The survival outcomes like LRC, disease free survival (DFS) and OS are comparable with 3D-CRT [13,14].

The Alterio meta-analysis also proved this fact that IMRT improves therapeutic ratio by reducing toxicity without any worsening clinical outcomes like death (srandardized rate ratio (SRR) = 0.93; 95% CI 0.83–1.04) and relapse (SRR = 0.92; 95% CI 0.83–1.03) compared to conventional techniques like 2D/3D-CRT [15].

The discussion as to whether a sequential schedule of IMRT is better than SIB-IMRT, was reviewed by the meta-analysis of Jiang et al., which reported no significant differences in OS (P = 0.071; HR 0.94) and locoregional failure (P = 0.91, HR 0.98) for head and neck squamous cell carcinomas [16]. However, a recent report by Felice et al. contradicts this review and indicates that SIB-IMRT improves OS and DFS compared to sequential IMRT [17]. The use of SIB-IMRT facilitates individual dose painting, thereby enabling treating different target volumes with different doses in the same treatment window which reduces treatment time as well [7,8].

Garden et al. published one of the largest series of 776 OPCs treated with IMRT with 93% stage III/IV cancers. However, only 41% received concurrent CHRT. The radiation dose range was 66 to 70–72 Gy, depending upon the stage. They reported significant difference in actuarial 5-year survival rate between the tonsil, the base of tongue and other sites (P < 0.001). Our cohort did not had a significant difference between different sites and also in comparison of the tonsil vs. others. There were only 26 regional recurrences. These rates are comparable with the cohort with only 17 regional recurrence events [18].

Various fractionation schedules have been tried in pharyngeal cancers. We have used 2.2 Gy per fraction. Similar fractionation (65 Gy / 30 fractions) has been used by Bird et al. in a report of 177 cases [19]. They used induction chemotherapy in 41% cases and had 72% stage IV cases. Their 3-year reported OS and DFS were 77.2 and 72.3%, respectively. Maqsood et al. reported IMRT outcomes in OPCs in 90 patients with 83% stage IV cases [20]. They reported 3-year OS rates of 77%. Our 4-year OS rates were 81.3%. The possible reason may be a lower number of locally advanced cancers with 38% stage IV cases. Wichmann et al. using 66 Gy at 2.2 Gy per fraction, 62.4 Gy at 2.08 per fraction and 54 Gy at 1.8 Gy per fraction reported 3-year LC of 73%, which is similar to our 4-year LC rate of 68% [7]. Montejo et al. described SIB-IMRT with 43 cases using 67.5 Gy in 33 fractions at 2.25 Gy per fraction and 60 and 54 Gy in lower-risk volumes. With a median follow-up of 36.7 months, they reported 2-year OS of 65% [21]. Gupta et al. compared 70 Gy / 35 fractions in 3D-CRT with 66 Gy at 2.2 Gy per fraction, 60 Gy and 54 Gy IMRT, both with concurrent chemotherapy in 60 patients. With a long median follow-up of 140 months, they did not find any significant difference in 10-year outcomes and significantly reduced grade 2 plus xerostomia and subacute fibrosis [22].

Chao et al. enumerated outcomes of OPCs with concurrent chemotherapy and IMRT in a study of 74 definitively treated patients. They used fractionation of 70 Gy / 35 fractions, 63 Gy / 35 fractions and 56 Gy / 35 fractions [23]. They reported 4-year LRC rates of 38%. Our results compare favorably with the study outcomes, possibly because all the cases in the study of Chao et al. were stage III and IV cases, and possibly because of the use of SIB schedule, while Chao et al. used standard fractionation IMRT. Dragan et al. recently published IMRT outcomes with 70 Gy / 35 fractions and 56 Gy /35 fractions to high- and low-risk volumes, respectively [8]. Three-year LRC and OS were 64 and 52%, respectively. Our 4- year results compare favorably with the cohort possibly because they included non-operable oral cavity malignancies as well, which portend poor prognosis.

Studer et al. was one of the first to use 2.2 Gy / fraction in pharyngeal cancers [24]. They found SIB-IMRT safe and tolerable in terms of acute and late tissue reactions when compared with 3-dimensional conformal radiotherapy. Their cohort had 52% stage III/IV cases and 23% N2c/3 cases. They reported 2-year local and nodal failure-free survival of 77 and 87%, respectively. Our results compare favorably with the outcomes in terms of nodal failures. The possible cause can be due to a lower number of nodal disease with N2c plus status.

Setton et al. reported the Memorial Sloan Kettering Cancer Center experience with 442 cases of OPCs treated with IMRT with median prescription doses of 70 Gy / 33 fractions at 2.12 Gy per fraction [25]. They reported 3-year OS of 89% with 94.6% stage III/IV cases. All local failures happened within 24 years with a median time to local failure of 9 months. They found significant difference between 3-year OS for N0,1 vs. N2,3 with P value of 0.01 (69.4 vs. 30.6%). We did not find any significant difference between N0,1 vs. N2,3 for 4-year LRC rates (69 vs. 64.3%; P = 0.639) and 4-year OS (83.6 vs. 92.3%). The possible reasons may be a lower number of N2 plus cases in our cohort. However, we reported significant difference in regional control values for N0 vs. N+ cases for both uni-variate and multivariate analysis (P = 0.039 in multivariate analysis).

Daly et al. published a study of 107 OPC cases with a median follow-up of 29 months with 96% stage III and IV cases. The fractionation schedules used were 66 Gy at 2.2 Gy / fraction, 54 Gy at 1.8 Gy / fraction and 50–52 Gy at 1.67–1.73 Gy / fraction [3]. On multivariate analysis, T4 had worse outcomes as compared to T1–3 for OS (P = 0.0036) and DFS (P < 0.0001). The younger age group (< 47 years) had improved OS (P = 0.0053) and DFS (P = 0.0083). The OS and LRC outcomes were not significantly different in our study, when analyzed for ≤ 50 vs. > 50 years, 4-year OS was 83.3 vs. 84.2% (P = 0.677). One of the possible causes may be the fact that only 28.4% cases were younger than 50 years. No significant differences were found in the LC (67.2 vs. 67.6%; P = 0.69) or OS (86.8 vs. 80.1%; P = 0.231) rates for stage T1, 2 vs. T3, 4. One of the probable causes for this may be a lack of HPV data which may have causes over-staging of P-16 positive cases.

Kimura et al. described oropharyngeal IMRT results of 93 patients. The cohort had a median follow-up of 40 months with 88% stage III/IV cases. The 3-year OS rates and LRC rates were 80 and 79%, respectively. Multivariate analysis revealed that patients with T3–4 stage of the disease and smoking history had significantly worse OS and LRC, respectively [26]. One of the drawbacks of the study was that 73% cases received induction chemotherapy, while only 21% received concurrent chemotherapy. The 3-year OS rates mentioned in this study and those stated by Huang et al. (3-year OS 83%) [14] and Sher et al. (3 year OS 86%) [27] are similar to the rates mentioned in the current review.

Singh et al. reported long term outcomes with IMRT in definitive manage-

ment of locally advanced head and neck squamous cell carcinoma not suitable for chemo-radiation. The 2-year estimated LRC and OS were 55.5 and 57.1%, respectively [28]. The possible reasons for relatively poor outcomes compared to our cohort may be relatively higher stages of pharyngeal tumors and non-administration of concurrent chemotherapy as defined in the protocol design.

Strengths and drawbacks of the study

The strengths of the study include a decent patient number, compared to the various reports published in the literature. Very few studies have reported IMRT outcomes with a larger number of patients. It is one of the largest reports of this kind from the Indian sub-continent. A major strength of the report is that the complete cohort was treated with standard concurrent CHRT protocols in line with the current guidelines. Our follow-up of 47.5 months is one of the longest when compared with the published literature. One of the drawbacks of the study is that it is a retrospective study. Another drawback is that the HPV analysis and smoking status was not contemplated for the patients due to limited availability of HPV status of the patients. A total of 5.4% patients were lost for a follow-up, which may have confounded the results slightly.

Conclusion

SIB-IMRT provides comparable outcomes for oropharyngeal cancers. Overall survival and loco-regional recurrences were significantly worse for nodal positive disease.

Ethics

Institutional ethical approval was taken for the study.

Financial Support

The research received no external funding.

Author contributions

All the authors contributed substantially to the study.

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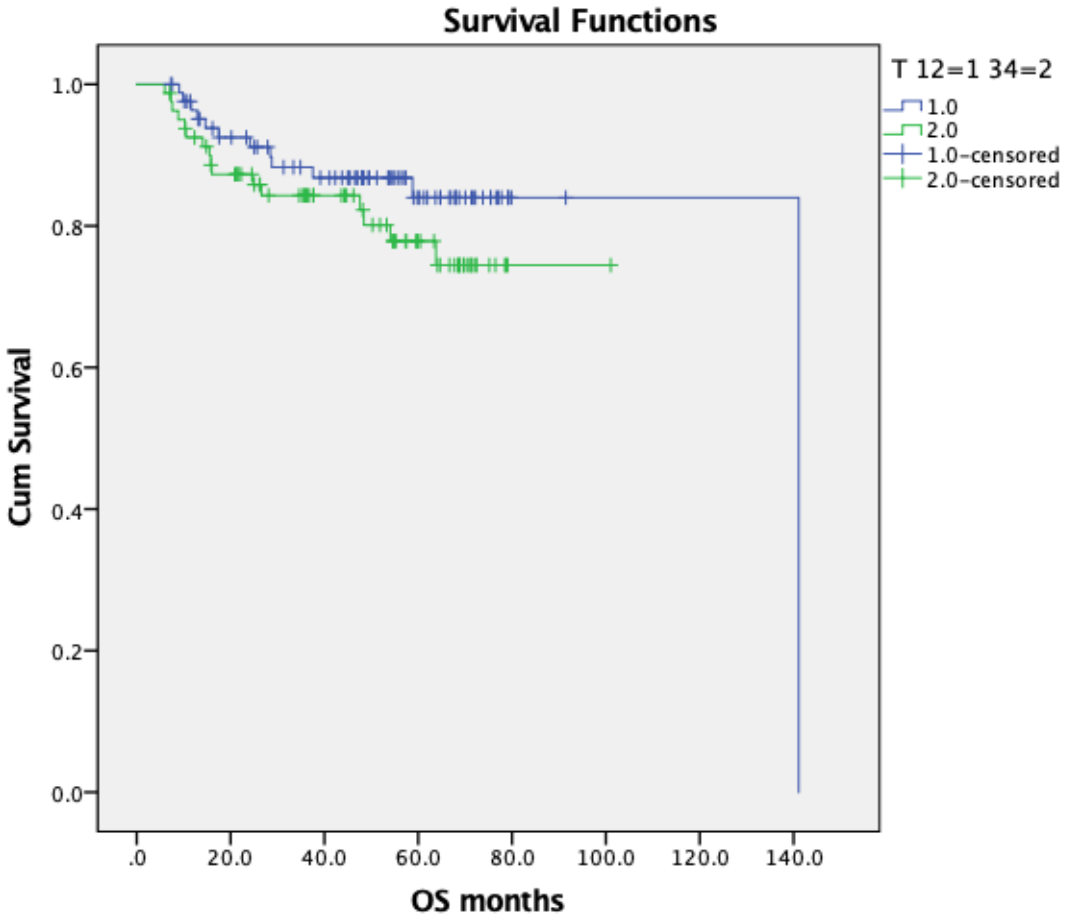
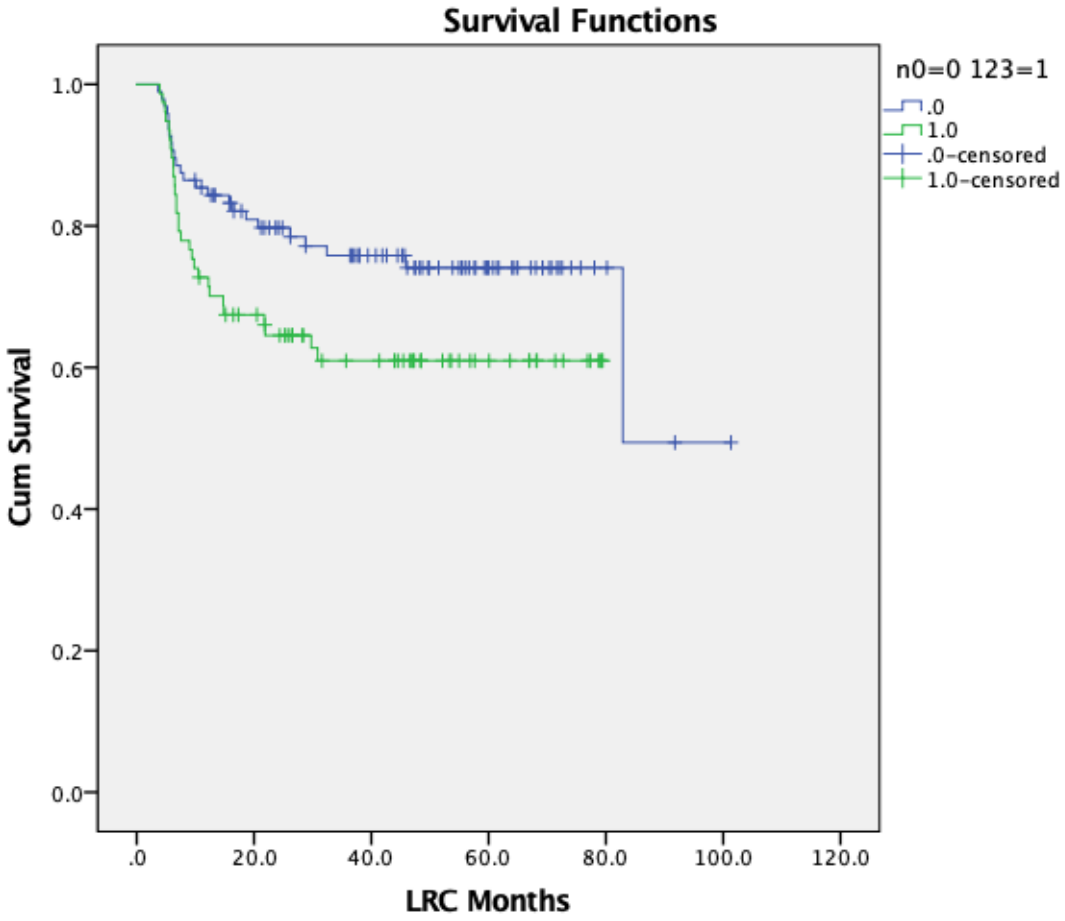
For graphs 1–3, see the online version of the article at www.linkos.cz.

Graph 1. Kaplan Meier Curve showing 4-year overall survival rates difference between early T stage vs. advanced T stage tumors (86.8 vs. 80.1%, P = 0.231).



Graph 2. Kaplan -Meier curve showing 4-year loco-regional control difference between N0 vs. N+ tumors (74 vs. 61%, P = 0.048).



Graph 3. Cox regression multivariate analysis showing 4-year regional control rates difference between N0 vs. N+ stage tumors (P = 0.039; HR –0.334; 95% CI 0.118–0.948).