RESEARCH ARTICLE

Postoperative radiotherapy with docetaxel versus cisplatin for high-risk oral squamous cell carcinoma: a randomized phase II trial with exploratory analysis of ITGB1 as a potential predictive biomarker

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Abstract

Background Oral squamous cell carcinoma (OSCC) causes significant mortality and morbidity worldwide. Surgical resection with adjuvant radiotherapy remains the standard treatment for locally advanced resectable OSCC. Results from landmark trials have established postoperative concurrent cisplatin-radiotherapy (Cis-RT) as the standard treatment for OSCC patients with high-risk pathologic features. However, cisplatin-related toxicity limits usage in clinical practice. Given the need for effective but less toxic alternatives, we previously conducted a single-arm trial showing favorable safety profiles and promising efficacy of concurrent docetaxel-radiotherapy (Doc-RT).

Methods In this randomized phase 2 trial, we aimed to compare Doc-RT with the standard Cis-RT in postoperative OSCC patients. Eligible patients had AJCC stage III–IV resectable OSCC with high-risk pathologic features. Two hundred twenty-four patients were enrolled and randomly assigned to receive concurrent Doc-RT or Cis-RT. The primary endpoint was 2-year disease-free survival (DFS). Secondary endpoints included overall survival (OS), locoregional-free survival (LRFS), distant metastasis-free survival (DMFS), and adverse events (AEs). Integrin β1 (ITGB1) expression was analyzed as a biomarker for efficacy.

Results After a median 28.8-month follow-up, 2-year DFS rates were 63.7% for Doc-RT arm and 56.1% for Cis-RT arm ($p = 0.55$). Meanwhile, Doc-RT demonstrated comparable efficacy to Cis-RT in OS, LRFS, and DMFS. Doc-RT resulted in fewer grade 3 or 4 hematological AEs. Low ITGB1 was associated with improved Doc-RT efficacy versus Cis-RT.

Conclusions This randomized trial directly compared Doc-RT with Cis-RT for high-risk postoperative OSCC patients, with comparable efficacy and less toxicity. ITGB1 merits further validation as a predictive biomarker to identify OSCC patients most likely to benefit from Doc-RT. Findings indicate docetaxel may be considered as a concurrent chemoradiation option in this setting.

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Background

Oral squamous cell carcinoma (OSCC) is one of the most commonly diagnosed cancers worldwide [1]. Surgical resection with adjuvant radiotherapy (RT) remains the standard treatment for locally advanced OSCC [1–4]. Results from two landmark randomized controlled trials in patients with head and neck squamous carcinoma (HNSCC), including OSCC, have consolidated concurrent cisplatin with radiotherapy as the standard treatment for patients with high-risk pathologic features after surgical resection [5, 6]. Research studies involving extensive cohorts of HNSCC have revealed that the presence of multiple lymph node metastases, in conjunction with classic high-risk features such as extracapsular nodal extension (ENE) and positive surgical margins, portend a substantially elevated risk profile, with postoperative chemoradiotherapy (CRT) conferring a survival benefit over RT alone in OSCC patients [7–9]. However, cisplatin-related adverse events (AEs) such as myelosuppression and nephrotoxicity remain major concerns, which have limited the real-world clinical usage of concurrent cisplatin [5, 6, 10, 11]. No pharmacologic agent has yet been identified that mitigates the acute toxicity of concurrent cisplatin-based chemoradiotherapy without negatively impacting the tolerability and efficacy of this combined modality regimen.

Docetaxel has exhibited promise as a radiosensitizing agent [12]. It has been hypothesized to enhance the effects of radiotherapy by inducing cell cycle synchronization in the highly radiosensitive G2/M phase, as well as by modulating the expression of various genes involved in the cellular radiation response [13, 14]. Multiple phase II trials have indicated that concurrent docetaxel-radiotherapy is tolerable and achieves favorable response rates in patients with HNSCC [15–17]. Recently, a single-center phase II/III trial by Patil et al. demonstrated that docetaxel could act as a radiosensitizer in HNSCC patients who are ineligible for cisplatin [18]. However, for cisplatin-eligible postoperative HNSCC patients, there remains a paucity of studies investigating alternatives to cisplatin for concurrent chemotherapeutic regimens. In our previous single-arm phase II trial comprising OSCC patients with high-risk features, concurrent docetaxel with radiotherapy demonstrated favorable toxicity profiles and achieved improved disease-free survival (DFS) and overall survival (OS), compared to the outcomes reported in the historical study (RTOG-9501) utilizing a cisplatin-based chemoradiotherapy [19]. These promising results prompted us to consider docetaxel as a potentially effective and better-tolerated option for concurrent chemotherapy in cisplatin-eligible patients.

Determining predictive biomarkers through pharmacogenomics is imperative for understanding response heterogeneity and enabling personalized therapy in cancer [20]. Previously, our integrated pharmacogenomic study of OSCC combining multi-omics and drug screening revealed that elevated integrin β1 (ITGB1) expression mediated docetaxel resistance [21]. ITGB1 is a transmembrane receptor protein that regulates diverse processes involved in chemoresistance and radioresistance [22]. Its intracellular domain contains a microtubule-binding region that interacts with microtubule proteins [23]. Activation and binding of ITGB1 can stabilize the microtubule cytoskeleton, while its inhibition leads to microtubule depolymerization [24, 25]. Given these interactions modulating docetaxel response, further investigation of the relationships between ITGB1 expression and clinical characteristics in docetaxel-treated OSCC patients may provide additional insights into biomarker-based treatment selection and design of chemoradiotherapy regimens. Detailed profiling of the ITGB1 landscape and its predictive power holds promise to inform personalized strategies and improve patient outcomes in OSCC. Based on the research results mentioned above, we initiated a prospective, open-label, randomized trial aimed at evaluating the efficacy of docetaxel-radiotherapy (Doc-RT) compared with the standard cisplatin-radiotherapy (Cis-RT) in cisplatin-eligible OSCC patients. Further, we present a prespecified biomarker assessment of the potential association between tumor ITGB1 expression and efficacy of Doc-RT versus Cis-RT in the trial.

Methods

Study design

This study was a phase II, open-label, single-center, randomized trial conducted at Shanghai Ninth People's Hospital. The protocol was approved by the Ethics Committee of Shanghai Ninth People's Hospital and registered at Clinicaltrials.gov (NCT02923258, CRTI number: 2016–129-T78). All patients provided written informed consent to participate in the study. The study was approved by our institutional ethics committee and was monitored by the data safety and monitoring

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subcommittee. The trial was conducted according to the principles laid down by the 18th Helsinki World Medical Assembly.

Patients and eligibility criteria

Eligible patients include patients who had stage III or IV OSCC according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. Patients had at least one pathologic high-risk factor including ENE, positive margins, and/or involvement of two or more regional lymph nodes. Eastern Cooperative Oncology Group (ECOG) performance status 0–1; aged 18–75 years.

Randomization

Patients were stratified according to pathological features (positive margin and/or ENE vs. ≥ 2 positive lymph nodes) and randomly assigned in a 1:1 ratio to receive either concurrent chemoradiotherapy with cisplatin or docetaxel. Randomization was performed centrally using a computer-generated sequence with randomly permuted block sizes.

Postoperative chemoradiotherapy

All patients were immobilized in thermoplastic head-and-shoulder masks with treatment-planning CT scans for defining target volumes. The target volumes and radiation doses were determined based on clinical information, physical examination, and contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). Postoperative intensity-modulated radiotherapy (IMRT) was delivered at 5 days per week over 6–7 weeks, to a total dose of 60–66 Gy (200 cGy/fraction/day). Clinical target volumes (CTV) were delineated as follows: CTV60 (60 Gy dose) covered high-risk target volumes, CTV54 (54 Gy dose) for low-risk regions, and a CTV6 boost (6 Gy dose) was added for positive margin and/or ENE, at the discretion of the treating radiation oncologist. Planning target volume (PTV) was defined as the CTV plus a 5-mm margin to account for potential variabilities in treatment setup and internal organ motion. Radiotherapy planning and delivery followed standardized departmental protocols.

In the Doc-RT arm, patients received intravenous (IV) docetaxel at 20 mg/m^2 weekly for six cycles during the RT period. In the Cis-RT arm, patients received cisplatin at a dose of 100 mg/m^2 IV every 3 weeks. Patients received routine hydration for the Cis-RT group. All patients received prophylactic antiemetic medications. Before the administration of chemotherapy, dexamethasone (at a dose of 5 mg or the equivalent) was given intravenously in both groups.

Chemotherapy was administered concurrently with radiotherapy until the last day of radiotherapy, but not beyond. Concurrent chemoradiotherapy was only given to patients with adequate bone marrow function (absolute neutrophil count ≥ 1.5 × 10^9/L; hemoglobin ≥ 10 g/dL) and adequate liver and kidney function (aspartate transaminase and alanine transaminase ≤ 2.5 × institutional upper limit of normal (ULN); total bilirubin ≤ institutional ULN; creatinine clearance ≥ 50 mL/min; serum creatinine ≤ institutional ULN). Administration of docetaxel/cisplatin was withheld for grade 4 mucositis or dermatitis, dehiscence of surgical incision, grade 3 anemia, and grade 3 neutropenia. Docetaxel was discontinued permanently for grade 4 hypersensitivity reactions. Dose modifications included reduction of docetaxel to 15 mg/m^2/week and cisplatin to 80 mg/m^2 if toxicities occurred.

Assessments

During the study, patients underwent assessments including physical examination and blood tests every week. Oncological assessments including physical examination, CT or MRI imaging of the head and neck, and CT or ultrasound imaging of the upper abdomen were mandated every 3 months for the first 2 years, every 6 months from years 2 to 5, and annually thereafter. All patients were intended to be followed until death for data collection and analysis. AEs were summarized and recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 weekly during the treatment. Acute AEs were analyzed in patients who received at least one administration of cisplatin or docetaxel.

Study endpoints

The primary endpoint was a 2-year DFS, defined as the time from randomization to the first recurrence or death from any cause. Secondary endpoints included OS, locoregional failure-free survival (LRFS), distant metastasis-free survival (DMFS), and AEs. OS was defined as the time in months between the date of random assignment and the date of death from any cause. LRFS was defined as the time in months between random assignment and the date of first locoregional recurrence or death from any cause, whichever occurred first. DMFS was defined as the time from random assignment to the first distant metastasis or death from any cause. Additional analysis includes subgroup analysis regarding survival outcomes.

ITGB1 expression

Immunohistochemistry (IHC) staining was carried out on full slides of Formalin-Fixed, Paraffin-Embedded (FFPE) tumor specimens as previously described, as

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per the manufacturer's instructions for ITGB1 (1:200, Cat#9699, Cell Signaling Technology) staining [21]. Images were captured using the ZEISS Axioscan 7 Microscope Slide Scanner. Results were interpreted by a certified pathologist using a standardized scoring algorithm involving the evaluation of the entire tissue slide. The staining intensity (negative = 0, weak = 1, moderate = 2, strong = 3) and percentage of positive tumor cells (0% = 0, 1–10% = 1, 11–50% = 2, 51–80% = 3, 81–100% = 4) were evaluated. An immunoreactive score (IRS) ranging from 0–12 was calculated by multiplying the numeric staining intensity and percentage. In previous studies, we divided patients into low and high expression groups based on the median value [21]. Considering a considerable number of intermediate expression samples, we refined the ITGB1 categorization in this study, dividing patients into three groups: low, medium, and high. The following ITGB1 expression categories were used: IRS 0 to < 3: ITGB1 low; IRS 3 to < 6: ITGB1 medium; IRS 6 to 12: ITGB1 high.

Sample size and statistics

The sample size was estimated to provide 80.2% power to detect a hazard ratio of 0.5788 for the improvement in DFS, using a two-sided log-rank test at a 0.050 significance level [26], accounting for a 10% loss to follow-up. A total of 224 subjects (112 per arm) were required, which could detect an improvement in 2-year DFS from 54 to 70%, assuming 54% 2-year DFS in the control arm based on the RTOG-9501 cohort [6]. The accrual pattern comprises a 3-year accrual period and a minimum 2-year follow-up.

Survivals were estimated by the Kaplan-Meier method and compared using the log-rank test. Cox models estimated hazard ratios (95% confidence interval [CI]) for subgroup analyses. ITGB1 subgroup treatment outcomes were compared using *t*-tests or Wilcoxon tests. Analyses used SPSS version 27. Intention-to-treat (ITT) analysis was used for survival, per-protocol for AEs. *P*-values assessed treatment difference significance at 0.05 level.

Results

Baseline characteristics

Between April 2018 and February 2022, a total of 224 patients were enrolled in this randomized controlled trial. The baseline characteristics of the study participants are summarized in Table 1. The consolidated standards of reporting trials (CONSORT) flow diagram delineating patient recruitment and retention is outlined in Fig. 1. High-risk features included positive surgical margins and/or ENE, and two or more metastatic lymph nodes. Baseline demographic and clinical parameters were balanced between the two treatment arms. We conducted

Table 1 Patient characteristics

Variable	Doc-RT (*n* = 112)	Cis-RT (*n* = 112)
Age, No. (range)		
Median, years	59.5 (37–73)	56 (24–72)
Sex, No. (%)		
Male	68 (60.7)	86 (76.8)
Female	44 (39.3)	26 (23.2)
High-risk features, No. (%)		
Positive margin	6 (5.4)	1 (0.9)
ENE	57 (50.9)	63 (56.3)
Positive margin and ENE	6 (5.4)	6 (5.4)
Multiple lymph nodes	43 (38.4)	42 (37.5)
Subsite of oral cavity, No. (%)		
Tongue	57 (50.9)	60 (53.6)
Buccal	15 (13.4)	17 (15.2)
Mouth floor	13 (11.6)	11 (9.8)
Gingival	22 (19.6)	21 (18.8)
Hard palate	5 (4.5)	3 (2.7)
Habits, No (%)		
Smoking	47 (42.0)	58 (51.8)
Regular alcohol	31 (27.2)	34 (30.4)
Pathologic T stage, No. (%)		
T1	21 (18.8)	22 (19.6)
T2	53 (47.3)	39 (34.8)
T3	32 (28.6)	42 (37.5)
T4	6 (5.4)	9 (8.0)
Pathologic N stage, No. (%)		
N0	3 (2.7)	1 (0.9)
N2a	22 (19.6)	17 (15.2)
N2b	43 (38.4)	36 (32.1)
N2c	1 (0.9)	5 (4.5)
N3b	43 (38.4)	53 (47.3)
Total Stage, No. (%)		
III	22 (19.6)	16 (14.3)
IV	90 (80.4)	96 (85.7)

ENE Extranodal extension, *Doc-RT* Docetaxel-radiotherapy, *Cis-RT* Cisplatin-radiotherapy, *No.* Number

this study database locked on April 30, 2023, for final data analysis.

Treatment compliance and chemotherapy delivery

IMRT was administered to all patients. In Doc-RT and Cis-RT arm, 107 (95.5%) and 110 (98.2%) patients received at least 95% of the prescribed RT dose, respectively. Two patients in the Doc-RT arm and one in the Cis-RT arm had RT-interruption over 5 days. Four patients in the Doc-RT arm (one with hypersensitivity reaction and subsequently received weekly cisplatin) and one in the Cis-RT arm terminated RT early and received salvage surgery or systemic therapy due to tumor
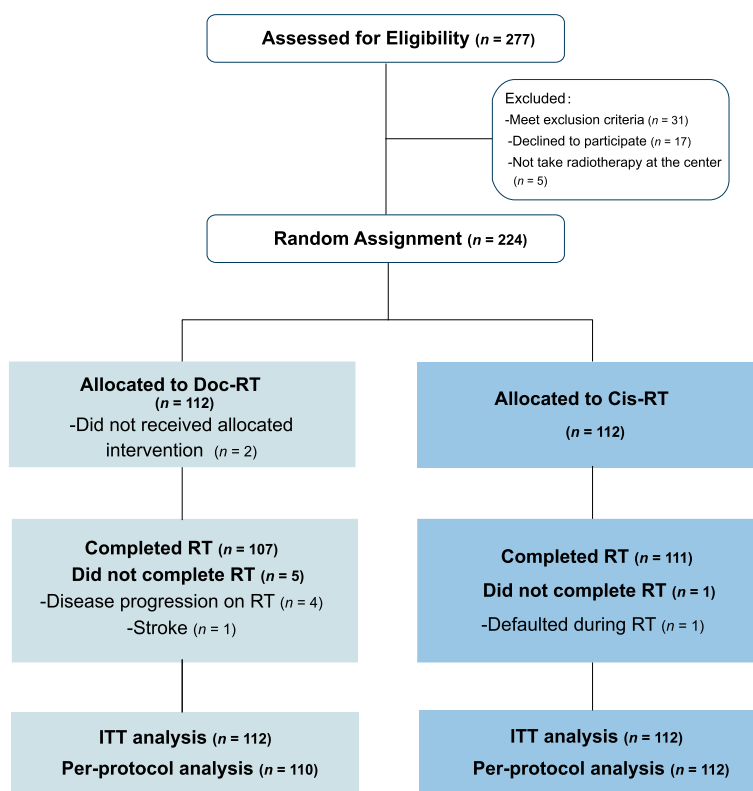
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Fig. 1 CONSORT diagram: enrollment, intent-to-treat and safety populations, and patient withdrawals. Doc-RT, docetaxel-radiotherapy; Cis-RT, cisplatin-radiotherapy; ITT, intention-to-treat; RT, radiotherapy

recurrence during treatment. RT for another patient in the Doc-RT arm was discontinued due to the need for emergency medical intervention following a cerebrovascular accident. The overall duration and interruptions of RT were comparable between the two arms (Table 2).

In the Doc-RT arm, two patients deviated from the prescribed regimen due to hypersensitivity reactions upon initial administration of docetaxel. Subsequently, these patients received weekly cisplatin as an alternative concurrent chemotherapy, per the discretion of the attending physician. Among the 107 patients in the docetaxel without early RT termination, 95 (88.8%) were administered at least five doses of docetaxel, with one patient requiring dose modification. In the Cis-RT arm, 103 of the 112 patients received at least two cycles, with 41 requiring dose modifications. The compliance details for each treatment group are presented in Table 2.

Survival
After a median follow-up of 28.8 months (interquartile range (IQR): 17–49 months), 98 DFS events occurred, with 47 in the Doc-RT arm (25 local regional progressions (LRP), 15 distant metastases (DM), 4 LRP with DM, 1 s primary tumor (SPT) and 2 deaths as first events) and

51 in the Cis-RT arm (including 27 LRP, 15 DM, 5 LRP with DM, 1 SPT and 4 deaths as first events). The 2-year DFS was 63.7% (95% CI, 55.2% to 73.2%) in the Doc-RT arm versus 56.1% (95% CI, 49.3% to 67.7%) in the Cis-RT arm ($p = 0.55$; Fig. 2A). The hazard ratio (HR) of DFS for docetaxel versus cisplatin was 0.92 (95% CI, 0.61 to 1.4). Median DFS were not reached in both groups.

Overall, 72 deaths occurred, with 34 in the Doc-RT arm and 38 in the Cis-RT arm. Median OS was not reached in both arms. The 2-year OS was 71.2% (95% CI, 61.5% to 78.8%) for the Doc-RT arm versus 70.4% (95% CI, 61% to 78%) for the Cis-RT arm ($p = 0.56$, Fig. 2B). The HR of OS for docetaxel versus cisplatin was 0.87 (95% CI, 0.55 to 1.38). The 2-year LRFS rate was 76.4% for the docetaxel arm versus 71.5% for the cisplatin arm (Fig. 2C). For DMFS, the 2-year rate was 81.9% in the docetaxel arm versus 77.9% in the cisplatin arm (Fig. 2D).

In a subgroup analysis, the HR of DFS for docetaxel versus cisplatin was 0.41 (95% CI, 0.18 to 0.91, $p = 0.028$) among patients with two or more metastatic lymph nodes, indicating an advantage for the Doc-RT arm (Fig. 3A). Subgroup analyses of other subgroups did not demonstrate any statistically significant differences between the two treatment arms with respect to DFS and

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Table 2 Compliance details for CRT

Parameter	Doc-RT (*n* = 112)	Cis-RT (*n* = 112)
Reason for termination of RT, No. (%)		
Disease progression	4 (3.57)	1 (0.89)
Patient defaulted	0 (0)	1 (0.89)
Stroke	1 (0.89)	0 (0)
Treatment duration, days, median (IQR)	45 (40–45)	45 (40–45)
Patients with interruption of RT, No. (%)		
Any interruption	34 (30.36)	37 (33.04)
Interruption over 5 days	2 (1.79)	1 (0.89)
AEs leading to interruption of RT over 5 days, No. (%)		
Oral mucositis	2 (1.79)	0 (0)
Surgical wound dehiscence	0 (0)	1 (0.89)
Reasons for < 5 cycles of docetaxel or < 2 cycles of cisplatin, No. (%)		
Myelosuppression	2 (1.79)	4 (3.57)
Oral mucositis	5 (4.46)	0 (0)
Defaulted	0 (0)	2 (1.79)
Disease progression	3 (2.68)	1 (0.89)
COVID-19 disease	2 (1.79)	0 (0)
Malnutrition	1 (0.89)	2 (1.79)
Stroke	1 (0.89)	0 (0)
Herpes zoster infection	1 (0.89)	0 (0)

CRT Chemoradiation, *Doc-RT* Docetaxel-radiotherapy, *Cis-RT* Cisplatin-radiotherapy, *RT* Radiotherapy, *IQR* Interquartile range, *COVID-19* Coronavirus disease 2019, *AE* Adverse events, *No.* Number

OS (Fig. 3A–B). Further subgroup analysis of LRFS demonstrated an HR of 1.16 (95% CI, 0.63 to 2.12, $p = 0.567$) in the ENE and/or positive margins subgroup, and an HR of 0.49 (95% CI, 0.20 to 1.18, $p = 0.121$) in the multiple lymph node metastasis subgroup. The HR for DMFS was 1.19 (95% CI 0.75–1.91, $p = 0.735$) in the ENE and/or positive margin subgroup, and 0.20 (95% CI 0.04–0.97, $p = 0.105$) in the multiple lymph node metastasis subgroup.

ITGB1 expression and efficacy outcomes
Among the 224 patients treated with Doc-RT or Cis-RT, archival tumors were evaluated for ITGB1 expression in 206 patients (Doc-RT arm: 100; Cis-RT arm: 106). In the Doc-RT cohort, 39 patients (39%) displayed low IRS for ITGB1, while 20 (20%) and 41 (41%) had medium and high IRS, respectively. A similar distribution of ITGB1 expression was observed in the Cis-RT cohort, with 44 (41.5%), 21 (19.8%), and 41 (38.7%) patients exhibiting low, medium, and high IRS, respectively.

Stratified by ITGB1 expression level, Doc-RT treated patients with low, medium, and high expression exhibited 2-year DFS of 73.8% (95% CI 56.7 to 84.99%), 75.0% (95% CI 50.0 to 88.7%) and 48.7% (95% CI 32.8 to 62.8%), respectively. In comparison, Cis-RT treated patients with corresponding low, medium, and high ITGB1 expression

had 2-year DFS of 54.5% (95% CI 38.7 to 67.7%), 52.4% (95% CI 29.7 to 70.9%) and 58.5% (95% CI 42.0 to 71.8%), respectively (Fig. 4A). Among Doc-RT patients, low ITGB1 expression was associated with improved prognosis compared to high expression, including significantly higher 2-year DFS (73.8% vs 48.7%; $p = 0.016$, Fig. 4A), and numerically but not significantly elevated 2-year OS (79.0% vs 60.9%; $p = 0.083$, Fig. 4B), locoregional relapse-free survival, and distant metastasis-free survival. No prognostic correlation with ITGB1 expression was evident in the Cis-RT cohort (Fig. 4A–B).

Despite the limited sample size, the consistently superior survival across endpoints in the Doc-RT/low ITGB1 subgroup suggests this population may benefit more from Doc-RT than Cis-RT. Notably, the ITGB1 prognostic value was only evident in the Doc-RT arm, not Cis-RT. This indicates ITGB1 may act as a predictive biomarker to identify sensitive and resistant subgroups specifically for Doc-RT.

Adverse events
Adverse events (AEs) were analyzed by per-protocol analysis and are presented in Table 3. Regarding non-hematologic toxicities, the incidence of grade 3 oral mucositis was higher in patients treated with Doc-RT compared to Cis-RT (29.1% vs 19.6%, $\chi^2 = 2.69$, $p = 0.1$),
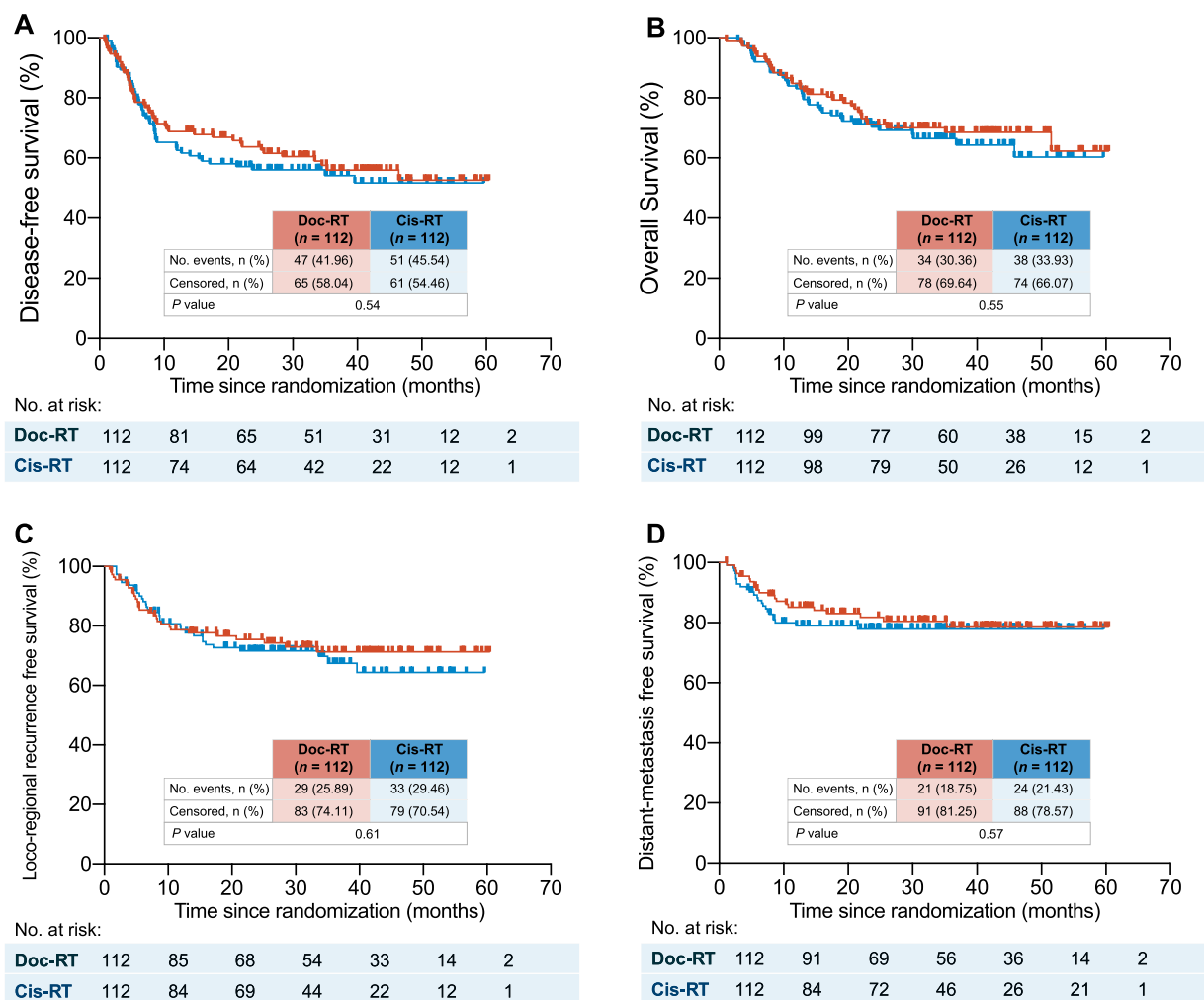
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Fig. 2 The Kaplan–Meier curve for DFS (**A**), OS (**B**), LRFS (**C**), and DMFS (**D**) for all randomly assigned patients. The symbols indicate censored observations. Doc-RT, docetaxel-radiotherapy; Cis-RT, cisplatin-radiotherapy; No., number

while grade 3 dysphagia occurred less frequently in the Doc-RT than the Cis-RT (5.5% vs 14.3%, $\chi^2 = 4.85$, $p = 0.028$). Oral candidiasis was detected in five patients receiving Doc-RT and one patient receiving Cis-RT. As for hematologic toxicities, 24 patients (21.4%) developed grade 3–4 neutropenia in the cisplatin arm, while only one patient in the Doc-RT arm exhibited grade 3 neutropenia ($\chi^2 = 23.38$, $p < 0.001$).

Discussion

In patients with OSCC exhibiting high-risk features, curative surgery with postoperative chemotherapy remains the standard method of reducing recurrence [27]. In this setting, concurrent high-risk cisplatin and RT have a modest OS benefit, but are associated with increased toxicities [28]. The purpose of this study was to compare the efficacy and safety of docetaxel as a concurrent chemotherapy regimen with high-dose cisplatin in

this population. Although this trial was not designed as a non-inferiority study, comparable oncological outcomes were demonstrated between the Doc-RT arm and the Cis-RT arm, including DFS, LRFS, DMFS, and OS. Additionally, the Doc-RT group experienced fewer hematological adverse events. This study also indicated that the ITGB1 status may be useful for identifying subgroups of patients who are sensitive to docetaxel.

For resectable high-risk OSCC, 3-weekly cisplatin at 100 mg/m^2 with postoperative RT is recommended by all international guidelines [29, 30]. Adding chemotherapy modestly improves OS at the expense of increased toxicities [5, 6]. Previous studies have demonstrated grade 3 or higher myelosuppression in approximately 49–78% of patients receiving high-dose cisplatin, requiring treatment delays and dose reductions [6, 31]. Consequently, due to the considerable AEs associated with cisplatin, there exists an unmet clinical need to
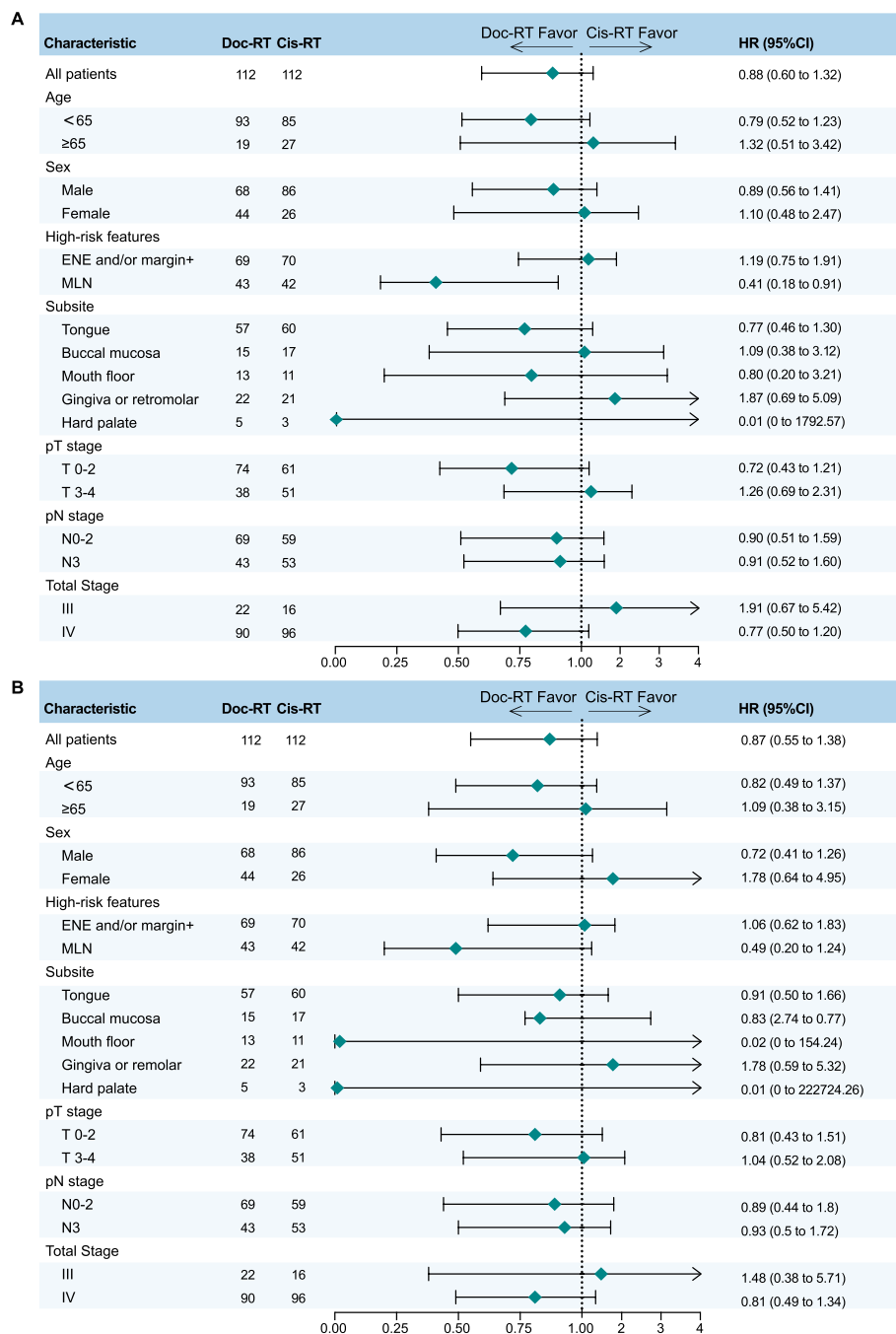
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A

Characteristic	Doc-RT	Cis-RT		HR (95%CI)
All patients	112	112		0.88 (0.60 to 1.32)
Age				
<65	93	85		0.79 (0.52 to 1.23)
≥65	19	27		1.32 (0.51 to 3.42)
Sex				
Male	68	86		0.89 (0.56 to 1.41)
Female	44	26		1.10 (0.48 to 2.47)
High-risk features				
ENE and/or margin+	69	70		1.19 (0.75 to 1.91)
MLN	43	42		0.41 (0.18 to 0.91)
Subsite				
Tongue	57	60		0.77 (0.46 to 1.30)
Buccal mucosa	15	17		1.09 (0.38 to 3.12)
Mouth floor	13	11		0.80 (0.20 to 3.21)
Gingiva or retromolar	22	21		1.87 (0.69 to 5.09)
Hard palate	5	3		0.01 (0 to 1792.57)
pT stage				
T 0-2	74	61		0.72 (0.43 to 1.21)
T 3-4	38	51		1.26 (0.69 to 2.31)
pN stage				
N0-2	69	59		0.90 (0.51 to 1.59)
N3	43	53		0.91 (0.52 to 1.60)
Total Stage				
III	22	16		1.91 (0.67 to 5.42)
IV	90	96		0.77 (0.50 to 1.20)

B

Characteristic	Doc-RT	Cis-RT		HR (95%CI)
All patients	112	112		0.87 (0.55 to 1.38)
Age				
<65	93	85		0.82 (0.49 to 1.37)
≥65	19	27		1.09 (0.38 to 3.15)
Sex				
Male	68	86		0.72 (0.41 to 1.26)
Female	44	26		1.78 (0.64 to 4.95)
High-risk features				
ENE and/or margin+	69	70		1.06 (0.62 to 1.83)
MLN	43	42		0.49 (0.20 to 1.24)
Subsite				
Tongue	57	60		0.91 (0.50 to 1.66)
Buccal mucosa	15	17		0.83 (2.74 to 0.77)
Mouth floor	13	11		0.02 (0 to 154.24)
Gingiva or remolar	22	21		1.78 (0.59 to 5.32)
Hard palate	5	3		0.01 (0 to 222724.26)
pT stage				
T 0-2	74	61		0.81 (0.43 to 1.51)
T 3-4	38	51		1.04 (0.52 to 2.08)
pN stage				
N0-2	69	59		0.89 (0.44 to 1.8)
N3	43	53		0.93 (0.5 to 1.72)
Total Stage				
III	22	16		1.48 (0.38 to 5.71)
IV	90	96		0.81 (0.49 to 1.34)

Fig. 3 Subgroup analysis of DFS (**A**) and OS (**B**) in all patients. Forest plot depicting the impact of the treatment effect on DFS (**A**) and OS (**B**) across multiple subgroups. Doc-RT, docetaxel-radiotherapy; Cis-RT, cisplatin-radiotherapy; ENE, extranodal extension; MLN, multiple lymph nodes; T, tumor; N, node; HR, hazard ratio; CI, confidence interval

identify novel radiosensitizers characterized by reduced toxicity profiles without compromising therapeutic efficacy. Our previous exploratory single-arm study demonstrated that concurrent weekly docetaxel at 20 mg/m^2 with adjuvant radiotherapy was well-tolerated and exhibited promising survival benefits compared to historical controls in high-risk OSCC [19]. This randomized trial further evaluated weekly docetaxel versus standard high-dose cisplatin with RT. As demonstrated in our study, grade 3–4 hematological and dysphagia rates were significantly lower with docetaxel, with similar oncological outcomes. Grade 3–4 oral mucositis
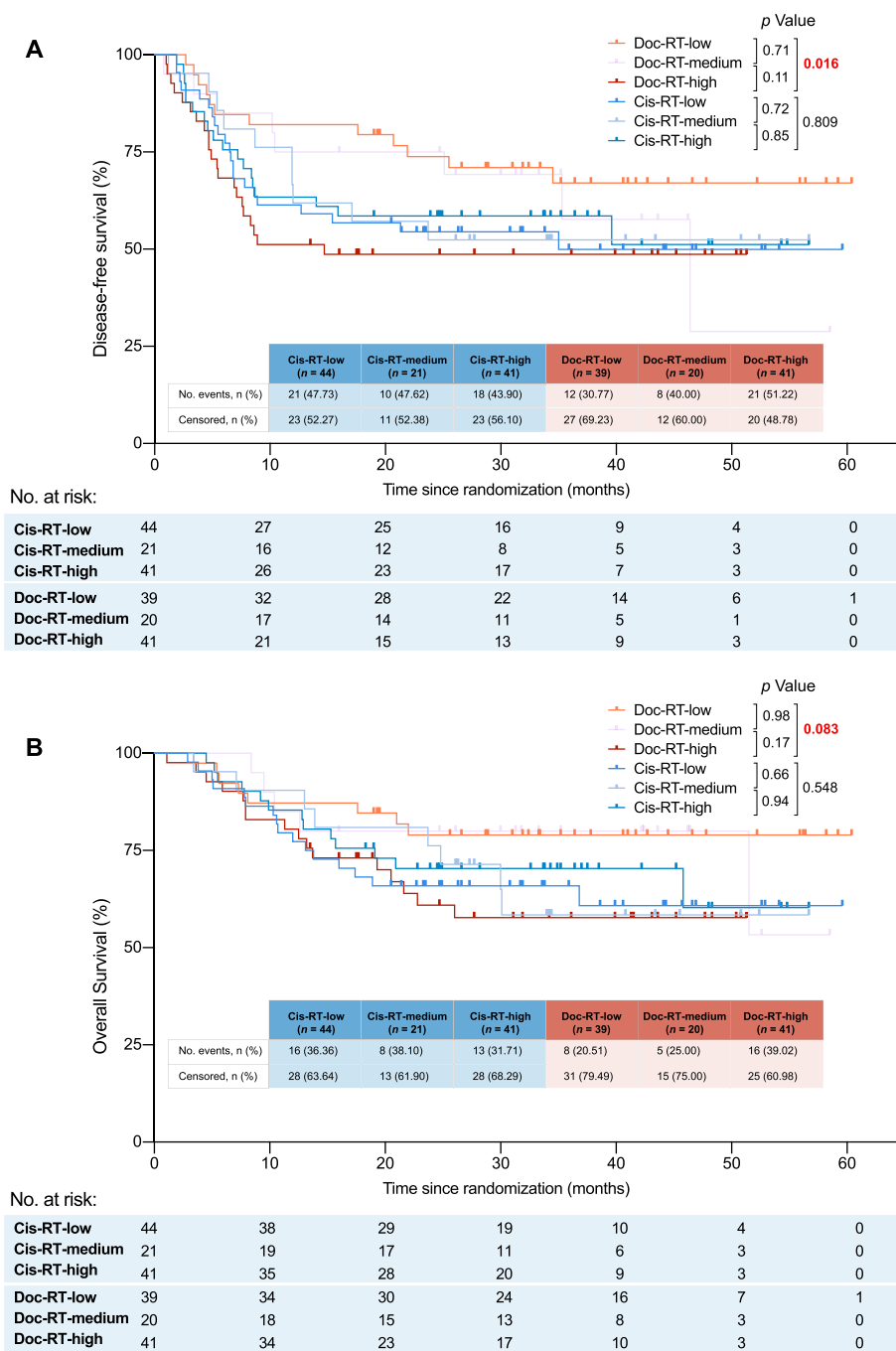
Fig. 4 ITGB1 expression and efficacy outcomes. **A** Disease-free survival by ITGB1 expression. **B** Overall survival by ITGB1 expression; ITGB1, integrin β1; Doc-RT, docetaxel-radiotherapy; Cis-RT, cisplatin-radiotherapy; No., number

occurred slightly more with docetaxel, but < 10% of patients required treatment modifications or discontinuation. Therefore, 20 mg/m² weekly docetaxel concurrently with postoperative RT could serve as a tolerable alternative for high-risk OSCC patients.

In recent years, several randomized controlled trials have explored the efficacy of docetaxel as concurrent chemoradiation for HNSCC. The RTOG-0234 phase II randomized trial investigated cetuximab-docetaxel versus cisplatin-cetuximab as concurrent regimens in

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Table 3 Treatment-related acute adverse events by assigned treatment

AE	Doc-RT (*n* = 110)		Cis-RT (*n* = 112)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Hematologic, No. (%)				
Anemia	47 (42.7)	0 (0)	93 (83)	14 (12.5)
Neutropenia	5 (4.5)	1 (0.9)	67 (59.8)	24 (21.4)
Thrombocyto-penia	2 (1.8)	0 (0)	8 (7.1)	1 (0.9)
Non-hematologic, No. (%)				
Mucositis	104 (94.5)	32 (29.1)	107 (95.5)	22 (19.6)
Dysphagia	51 (46.4)	6 (5.5)	67 (59.8)	16 (14.3)
Dermatitis	110 (100)	8 (7.3)	112 (100)	11 (9.8)
Nausea	13 (11.8)	0 (0)	59 (52.7)	5 (4.5)
Vomiting	5 (4.5)	0 (0)	15 (13.4)	1 (0.9)
Stroke	0 (0)	1 (0.9)	0 (0)	0 (0)
Raised creati-nine	1 (0.9)	0 (0)	32 (28.6)	0 (0)
ALT increased	3 (2.7)	0 (0)	31 (27.7)	3 (2.7)
AST increased	2 (1.8)	0 (0)	18 (16.1)	2 (1.8)

AE Adverse events, *Doc-RT* Docetaxel-radiotherapy, *Cis-RT* Cisplatin-radiotherapy, *No.* Number, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase

high-risk postoperative HNSCC patients [15]. Both regimens showed promising outcomes with improved DFS and OS compared to historical high-dose cisplatin controls [15]. However, the high cost of cetuximab and a greater than 50% rate of severe oral mucositis limit its practical clinical application. Notably, cetuximab-docetaxel with RT showed favorable DFS compared to cetuximab-cisplatin (65.9% vs 57.3%, respectively), implying that single-agent docetaxel may also lead to favorable survival. Therefore, we further investigated concurrent docetaxel in this current study. As shown in our findings, the 2-year DFS in the Doc-RT arm were comparable to those reported for the docetaxel-cetuximab-RT regimen in RTOG-0234, while exhibiting a lower frequency of grade 3–4 oral mucositis. The DHANUSH trial by Patil et al. was a randomized study in cisplatin-ineligible HNSCC patients, demonstrating that adding weekly 15 mg/m^2 docetaxel improved 2-year DFS compared to radiotherapy alone (42% vs 30%) [18]. However, the survival outcomes of concurrent docetaxel and radiotherapy in this trial appeared suboptimal compared to historical RTOG-9501 controls, with no statistically significant survival benefit with concurrent docetaxel in DFS and OS for adjuvant setting or OSCC patients [6, 18]. This could be attributed to the relatively low 15 mg/m^2 dose of docetaxel, which may have radiosensitizing effects but be insufficient for distant control of micrometastases. In light of our findings, a higher dose docetaxel regimen at 20 mg/m^2 concurrently with radiotherapy may represent a well-tolerated and efficacious option for postoperative concurrent chemoradiotherapy in high-risk OSCC patients.

It is noteworthy that this study specifically focused on OSCC, not other head and neck subsites with different survival expectations, like human papillomavirus (HPV)-related oropharyngeal cancer [32–34]. Firstly, surgery followed by postoperative radiotherapy (with or without chemotherapy) remains the standard treatment modality for OSCC [35], in contrast to definitive chemoradiation, which is widely employed for oropharyngeal cancer. Furthermore, although ENE and positive margins were considered conventional high-risk features based on two milestone studies [5, 6, 27], these trials included less than one-third of OSCC patients, potentially suggesting an incomplete consideration of high-risk factors in this specific population. Notably, recent analyses involving large cohorts have identified multiple lymph node metastases as an additional high-risk feature associated with adverse outcomes in HPV-unrelated HNSCC, such as OSCC [7–9]. Concurrent chemoradiotherapy has been demonstrated to improve prognosis for patients with multiple lymph node metastases [7, 8]. Consequently, our findings directly inform chemotherapy selection for postoperative chemoradiation in OSCC patients harboring these risk features. Additionally, all patients received IMRT, providing evidence for a concurrent chemotherapy regimen in the context of modern radiotherapy techniques.

Precision oncology promises to transform cancer treatment by accounting for the molecular heterogeneity of tumors between patients [36]. While standardized protocols remain the norm, biomarkers that predict patient-specific drug responses may enable personalized regimens with improved safety and efficacy [37, 38]. Previously, we found ITGB1 mediates resistance to docetaxel in OSCC models [21]. ITGB1 is implicated in multiple drug resistance mechanisms across cancers [39–41]. In OSCC cells, ITGB1 regulates cell stemness, which in turn modulates perineural invasion and radioresistance [42]. Our present clinical study newly demonstrates that ITGB1 expression correlates with docetaxel radiotherapy response in OSCC patients, whereas cisplatin sensitivity was independent of ITGB1 status. Looking ahead, molecular profiling of ITGB1 and other pharmacogenomic markers could potentially guide optimal personalized therapy selection for each patient.

It is imperative to acknowledge certain limitations. As a single-institution study, our findings may be constrained by the limited patient diversity and potential heterogeneity in radiotherapy planning practices compared to a multi-institutional setting, potentially restricting the generalizability of our results to broader patient populations. Additionally, the increasing adoption of weekly cisplatin

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regimens in recent years may introduce more variability in cisplatin administration schedules in real-world clinical practice [31, 43, 44], in contrast to the bolus triweekly cisplatin utilized as the control arm in this study. Consequently, large-scale, multi-institutional studies will be essential to validate these findings across diverse real-world patient populations and further investigate potential heterogeneity in clinical responses.

New strategies involving docetaxel are still being explored. The ongoing RTOG-1216 phase II/III trial will provide high-quality evidence on postoperative concurrent weekly docetaxel-cetuximab and cisplatin-PD-1 inhibitor chemoradiotherapy for high-risk HNSCC. Its results may inform the utility of docetaxel and cetuximab with postoperative radiotherapy [45]. Studies have combined immune checkpoint inhibitors with chemotherapy regimens to improve HNSCC outcomes. Given the potential ITGB1-docetaxel association indicated in our study, biomarkers like ITGB1 could help select patients for future regimens combining docetaxel and other agents.

Conclusions

In conclusion, this is the first prospective randomized trial directly comparing concurrent docetaxel-radiotherapy versus standard cisplatin-radiotherapy in the postoperative setting of OSCC patients. Although the primary endpoint was not achieved in this study, Doc-RT demonstrated comparable efficacy to the standard Cis-RT regimen, as measured by DFS, OS, LRFS, and DMFS. Severe hematological AEs were rarely observed in the Doc-RT group, and non-hematological AEs were generally manageable. ITGB1 may serve as a potential biomarker to help guide the selection of concurrent chemotherapy agents in these patients, warranting further investigation to elucidate the mechanisms involved and validation in larger global patient cohorts.

Abbreviations

AE	Adverse event
AJCC	American Joint Committee on Cancer
Cis-RT	Cisplatin-radiotherapy
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed tomography
CTV	Clinical target volumes
DFS	Disease-free survival
DMFS	Distant metastasis-free survival
Doc-RT	Docetaxel-radiotherapy
ECOG	Eastern Cooperative Oncology Group
ENE	Extracapsular nodal extension
FFPE	Formalin-Fixed Paraffin-Embedded
HNSCC	Head and neck squamous cell carcinoma
IHC	Immunohistochemistry
IMRT	Intensity-modulated radiotherapy
ITGB1	Integrin β1
LRFS	Locoregional-free survival
MRI	Magnetic resonance imaging
OS	Overall survival
OSCC	Oral squamous cell carcinoma
PTV	Planning target volume
RT	Radiotherapy

Authors' contributions
GZ designed the study. WJ, LC, RL, JL, SD, LY, ZT, YY, and GZ were responsible for patient recruitment, collection and analysis of clinical data, preparation of patient samples, or conducting biomarker detection and analysis. WJ, YY, LC, RL, SD, and HY performed statistical analysis and interpreted the data. WJ, YY, and LC reviewed the literature and drafted and revised the manuscript. All authors contributed to data interpretation and reviewed the manuscript for language and intellectual content. All authors read and approved the final manuscript.

Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to the participants not consenting to open access data sharing but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by the Ethics Committee of Shanghai Ninth People's Hospital and registered at Clinicaltrials.gov (NCT02923258, CRTI number: 2016–129-T78). All patients provided written informed consent to participate in the study. The study was approved by our institutional ethics committee and was monitored by the data safety and monitoring subcommittee.

Consent for publication
Not applicable.

Competing interests
No potential competing interests were reported by the authors.

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