Hypofractionated palliative volumetric modulated arc radiotherapy with the Radiation Therapy Oncology Group 8502 “QUAD shot” regimen for incurable head and neck cancer

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Abstract

Background : To review a single institutional experience of the Radiation Therapy Oncology Group (RTOG) 8502 “QUAD shot” regimen using volumetric modulated arc radiotherapy (VMAT) for incurable head and neck cancer (HNC).

Methods : Thirty-four consecutive patients with HNC were treated with at least 1 cycle of the RTOG 8502 regimen. Treatment plans included the use of VMAT with 6 MV photons generated by a linear accelerator. Two daily fractions of 3.7 Gy were delivered with an interval of at least 6 h for 2 consecutive days, totaling 14.8 Gy over 4 fractions. This was repeated every 3–4 weeks for a total of 3 cycles. No concurrent systemic therapy was performed.

Results : The number of completed cycles was 1 in 6 (18%) patients, 2 in 5 (15%), and 3 in 23 (68%). Tumor response was achieved in 29 (85%) patients and symptom relief in 20 (77%) of 26 patients. Overall response (tumor response or symptom relief) was achieved in 32 (94%) patients. All patients who received 2 or more treatment cycles achieved overall response. Median overall survival (OS) was 5.7 months. Multivariate analysis revealed that completion of all 3 treatment cycles was significantly associated with better OS (P = 0.002). Grade 2 toxicity was observed in 4 (12%) patients, but no acute or late toxicities of Grade ≥3 were observed.

Conclusions : The RTOG 8502 “QUAD shot” regimen using VMAT is effective for incurable HNC with highly reduced toxicities. Treatment with multiple cycles is recommended for better treatment response and/or survival.

Introduction

Patients with head and neck cancer (HNC) are often ineligible for curative therapy such as surgery and definitive radiotherapy (RT) because of advanced age, poor performance status, extent of the tumor, prior treatment, and comorbidities. Patients with HNC often have symptoms such as pain, hemorrhage, dysphagia, and airway compromise which decrease the quality of life (QOL) (1, 2).

RT for incurable HNC has been demonstrated to be an effective palliative modality, even for patients who have received prior RT (2, 3). Currently, no general consensus exists for appropriate palliative RT regimen in HNC. Generally, a once-daily hypofractionated RT regimen of 30 Gy/10 fractions is commonly performed as palliative RT regardless of the tumor site; however, this treatment regimen is not appropriate for HNC because of the acute adverse effects. The reported frequency of Grade 3 or higher acute toxicities with this treatment regimen for patients with HNC was more than 40% (4). Other hypofractionated palliative RT regimens have been reported for HNC. Stevens et al performed palliative RT for 148 patients with newly diagnosed HNC (5). The median RT dose and fraction number were 50 Gy and 20; the most frequently used fractionation regimen was a split course designed to deliver a total dose of 50 Gy in 2.5-Gy fractions within 6 weeks, composed of 2 cycles of 25 Gy in 10 fractions given within 2 weeks, separated by a 2-week break. Overall response was reported in 85 (57%) patients, while 10 (7%) and 8 (5%) patients had unplanned discontinuation and planned RT interruption because of the toxicities, respectively. The “Hypo Trial” conducted by Porceddu et al treated 35 incurable patients with HNC; patients received 30 Gy in 5 fractions at 2/week, at least 3 days apart, with an additional boost of 6 Gy for small volume disease (≤ 3 cm) in suitable patients (6). Tumor response was achieved in 28 (80%) patients. Grade 2 and 3 mucositis were reported in 13 (37%) and 9 (26%) patients, respectively, and Grade 2, 3 and 4 dysphagia were reported in 23 (66%), 4 (11%) and 2 (6%) patients, respectively. These RT regimens provide certain palliative response, however, acute adverse effects, which may decrease patients’ QOL, are still relatively strong.

In the 1980s, the Radiation Therapy Oncology Group (RTOG) performed a phase II study of RT, which consisted of 2 days of twice-daily fractionation with a fraction size of 3.7 Gy (14.8 Gy per cycle) repeated at 3 to 6 week intervals for a total of 3 cycles with an RT dose of 44.4 Gy for pelvic malignancies (7). Thereafter, this RTOG 8502 “QUAD shot” regimen has been successfully adapted for palliative treatment of HNC. The RTOG 8502 regimen for HNC has been reported to achieve tumor

response and palliation in approximate 50–85% and 55–100% of patients, respectively. Furthermore, toxicity has been reported to be mild, with Grade 3 toxicity for approximately 0–10% of patients (2, 4, 8–11).

In earlier studies, RTOG 8502 regimen was performed using a 2-dimensional (2D) RT. RT field was typically defined as the gross symptomatic disease plus a 1 to 2 cm margin based on the physical examination (8, 9). The technical development of RT techniques in the last 2 decades, such as 3-dimensional conformal RT (3D-CRT) and intensity-modulated radiotherapy (IMRT) based on the precise target definition using images of computed tomography (CT), provides an enhanced dose concentration to the target volumes and reduces the dose to organs at risk (OAR) (12, 13). The current National Comprehensive Cancer Network (NCCN) guidelines recommend the RTOG 8502 regimen using 3D-CRT or IMRT as one of the palliative RT regimens for HNC (14).

More recently, volumetric modulated arc therapy (VMAT) has been introduced to treat HNC (15). Using this technique, the gantry is rotated while the dose is being delivered, and 3 parameters (dose rate, field shape, and speed of gantry rotation) can be changed as the beam is rotated (16). Compared with conventional fixed-field IMRT, VMAT provides similar excellent dose coverage to the target volume with a reduced dose to OARs. Furthermore, the treatment time of VMAT is much shorter than conventional IMRT; the approximate treatment times are 2 to 4 and 10 to 15 minutes for VMAT and IMRT, respectively (15). Introduction of VMAT into palliative RT regimen with RTOG 8502 may provide good treatment response with reduced toxicities for patients with HNC. To the best of our knowledge, the treatment results of RTOG 8502 regimen using VMAT has not been evaluated. The purpose of this study was to review a single institutional experience of the RTOG 8502 “QUAD shot” regimen using VMAT for incurable HNC.

Materials And Methods

Patients

This retrospective study was approved by the institutional review board of our hospital. Prior informed consent for treatment was obtained from all patients. Between January 2018 and July 2019, 34 consecutive patients with HNC were treated with at least 1 cycle of palliative RT with the RTOG 8502 regimen. Eligible patients had histologically or cytologically proven malignancy from primary of head and neck origin or large nodal metastasis from an unknown primary suspected to be of head and neck origin. They were ineligible for definitive or systemic therapy due to disease extent, extensive comorbidity, or refusal to undergo conventional treatment; hence, no patients received concurrent systemic therapy during treatment. The minimum interval between prior RT and reirradiation with the RTOG 8502 regimen had to be 6 months.

Radiotherapy details and technique

Patients were simulated with planning CT imaging in a dedicated thermoplastic head and neck mask for immobilization prior to each RT cycle. Gross tumor volume (GTV) included primary tumor and lymph node metastases. A clinical target volume margin of 5 mm was added to the GTV for subclinical invasion. Planning target volume (PTV) margins of 3 mm were added to cover setup errors. Treatment plans included the use of VMAT (RapidArc; Varian Medical Systems, Palo Alto, CA, USA) with 6 MV photons generated by a linear accelerator (Clinac iX; Varian Medical Systems, Palo Alto, CA, USA). The plan was generated using 1 arc rotating from 181° to 179° clockwise with the dose rate varied between 0 MU/min and 600 MU/min.

RT was delivered using the RTOG 8502 “QUAD shot” regimen. Two daily fractions of 3.7 Gy were delivered with an interval of at least 6 h for 2 consecutive days, totaling 14.8 Gy over 4 fractions. This was repeated every 3–4 weeks for a total of 3 cycles and a total dose of 44.4 Gy. The goals of the VMAT plans for target volume were defined as follows: dose to 95% of the PTV (D_{95}) > 95% of the prescribed dose, the percentage of the PTV receiving 93% of the prescribed dose ($V_{93\%}$) > 99%, the percentage of the PTV receiving 110% of the prescribed dose ($V_{110\%}$) < 1%. The maximum allowable dose limit of the

spinal cord and brainstem was defined as a total dose of 30 Gy and 50 Gy for the patients without and with previous RT, respectively. The mean dose of each treatment cycle was < 5Gy for at least one parotid gland. The dose to the mucous membrane and skin, which were non-adjacent to the target volume was reduced as little as possible. The cone-beam CT (CBCT) scans were acquired using a kilovoltage CBCT scanner and images of CBCT were registered to planning CT for image guidance of each treatment session. For patients with 2 or more treatment cycles, adaptive radiothrapy (ART) was performed to adjust to their anatomic changes and to avoid overdosing of normal tissues and underdosing or marginal geographic misses of target volumes during a course of treatment by repeating planning CT imaging and replanning for every cycle.

Evaluation of treatment response and toxicity

Tumor response, symptom relief, and toxicity were assessed every 2 weeks until 1 month after the final course of treatment, and every 3 to 4 weeks thereafter until patients died or were no longer able to comply (9). Tumor response was evaluated by physical examination and/or radiographic tumor response, and defined as objective shrinkage of GTV (2, 4). Symptom relief was defined as subjective reduction of the presenting symptom(s) (2, 11). Overall response was defined as tumor response or symptom relief. Toxicity was scored by the Common Terminology Criteria for Adverse Events version 5.0. An acute toxicity was defined as occurring up to 3 months after treatment completion (2).

Statistical analysis

Overall survival (OS) and progression-free survival (PFS) rates were calculated from initiation of RT using the Kaplan-Meier method. Candidate variables for prognostic factors of OS and PFS, including age, Eastern Cooperative Oncology Group performance status, tumor site, histology, clinical stage, and treatment cycles were evaluated by univariate analysis using log-rank statistics. To determine the independent significance of variables, multivariate analyses were performed using the Cox proportional hazards model, by selecting significant variables on univariate analysis. Differences with *P*-values < 0.05 were considered statistically significant. Statistical calculations were performed using SPSS software, version 26.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient and treatment characteristics

Patient characteristics are summarized in Table 1. The majority of patients were 75 years or older (N = 25, 74%). The histology was squamous cell carcinoma in 28 (82%) patients, salivary duct carcinoma in 2 (6%), intestinal-type adenocarcinoma in 1 (3%), papillary carcinoma in 1 (3%), verrucous carcinoma in 1 (3%), and poorly differentiated carcinoma in 1 (3%). Seven (21%) patients had received prior RT at the palliative sites. The number of completed cycles was 1 in 6 (18%) patients, 2 in 5 (15%), and 3 in 23 (68%).

Table 1
Patient characteristics (N = 34)

Characteristics	N	(%)
Age (years)	Median 81 (range: 54–92)	
Gender		
Male	18	53
Female	16	47
ECOG performance status		
0	5	15
1	8	24
2	11	32
3	10	29
Tumor site		
Oral cavity	19	56
Nasal cavity and paranasal sinuses	5	15
Hypopharynx	4	12
Skin	2	6
Major salivary gland	2	6
Thyroid	1	3
Neck disease with an unknown primary	1	3
Histology		
Squamous cell carcinoma	28	82
Others	6	18
Clinical stage		
II	3	9
III	3	9
IVA	17	50
IVB	9	26
IVC	2	6
Abbreviations: ECOG = Eastern Cooperative Oncology Group		

Treatment response

Tumor response was achieved in 29 (85%) patients (Table 2). Twenty-six (76%) patients had pretreatment symptoms; the predominant presenting symptoms were pain (N = 24, 71%) and hemorrhage (N = 9, 26%). Symptom relief was achieved in 20 (77%) of the 26 patients. Overall response was achieved in 32 (94%) patients.

Table 2
Tumor response, overall response and toxicities according to completed cycles of Radiation Therapy Oncology Group 8502 regimen

Completed cycles	N	Response				Toxicity			
		Tumor response		Overall response		Grade 1		Grade 2	
		N	%	N	%	N	%	n	%
1	6	3	50	4	67	1	3	0	0
2	5	5	100	5	100	1	3	0	0
3	23	21	91	23	100	7	21	4	12
Total	34	29	85	32	94	9	26	4	12

Survival

At the time of analysis, 32 (94%) patients had died. The median follow-up duration was 5.8 (range: 1.0–18.9) months. Median OS was 5.7 (range: 1.0–18.9) months. Univariate analysis showed that clinical stage II-III ($P = 0.046$) and the completion of all 3 treatment cycles ($P = 0.003$) were significantly associated with better OS (Table 3, Fig. 1). These 2 factors remained as independent variables for OS in a multivariate analysis ($P = 0.023$ and $P = 0.002$, respectively). Median PFS was 4.4 (range: 0.8–15.9) months. The univariate analysis revealed that only the completion of all 3 treatment cycles was significantly associated with better PFS ($P = 0.045$, Table 3, Fig. 1).

Table 3
Univariate and multivariate analysis of the overall and progression-free survival

Variable	N	OS			PFS
		UVA	MVA		UVA
		P-value	HR (95% CI)	*P*-value	*P*-value
Age (years)					
<80	12	0.684	NA		0.265
≥80	22				
ECOG performance status					
0–1	13	0.375	NA		0.847
2–3	21				
Tumor site					
Oral cavity	19	0.627	NA		0.647
Others	15				
Histology					
SCC	28	0.886	NA		0.482
Others	6				
Clinical stage					
II-III	6	0.046	1	0.023	0.321
IV	28		1.922 (1.096–3.371)		
Cycles of RTOG 8502					
1–2	11	0.003	3.711 (1.652–8.340)	0.002	0.045
3	23		1		

Abbreviations: ECOG = Eastern Cooperative Oncology Group; SCC = squamous cell carcinoma; RTOG = Radiation Therapy Oncology Group; OS = overall survival; PFS = progression-free survival; UVA = univariate analysis; MVA = multivariate analysis; HR = hazard ratio; CI = confidence interval; NA = not applicable

Toxicity

Grade 1 acute toxicity was observed in 9 (26%) patients, with the most common being mucositis (N = 7) and dry mouth (N = 3). Grade 2 acute toxicity was observed in 4 (12%) patients, and consisted of mucositis (N = 4) and dry mouth (N = 1) (Table 2). No acute or late toxicities of Grade ≥ 3 were observed.

Discussion

Palliative RT should be considered for relief or prevention of locoregional symptoms; however, severe toxicities should be avoided (14). Our results suggested that RTOG 8502 regimen using VMAT is one of the strongest candidates of palliative RT regimens with good treatment response and low toxicities.

The clinical outcome of RT with RTOG 8502 regimen for patients with head and neck tumors is summarized in Table 4. Paris et al reported the results of phase I-II study of RTOG 8502 regimen without chemotherapy for incurable HNC in 1992 (8). They treated 37 patients with 39 lesions with 2D-RT technique using Cobalt 60 or 6 MV photons. The spinal cord dose was limited to 30 Gy by field reduction. Twenty-one (57%) patients completed all 3 cycles and tumor response was achieved in 30 (77%) of the 39 treated lesions. A decade later, Corry et al reported the results of phase II study of palliative RT with a similar QUAD shot regimen without chemotherapy for incurable HNC (9). They performed RT to a maximum of 3 cycles with a fraction size of 3.5 Gy, which differed slightly from the original RTOG 8502 regimen. Radiation was delivered using 2D-RT and the spinal cord was excluded to limit its dose to 28 Gy in 8 fractions. Sixteen (53%) patients completed all 3 cycles and 16 (53%) patients achieved a tumor response. Our tumor response results were superior to those achieved with 2D-RT. One of the reasons for this superiority may be that dose coverage for the target volume using VMAT is superior to that of 2D-RT because it is technically difficult to provide uniform distribution to the target volume using 2D-RT while reducing spinal cord dose within the limitation. Recently, Gamez et al reported treatement results of RTOG 8502 regimen in stage III–IV head and neck tumors (11). All 21 patients underwent concurrent systemic therapy: 18 (86%) and 3 (14%) patients received carboplatin and cetuximab, respectively. Radiation was delivered using a 3D-CRT in 6 (29%) patients and IMRT in 15 (71%) patients. Sixteen (76%) patients completed all 3 cycles and 18 (86%) patients achieved a tumor response. Although we did not perform concurrent systemic therapy, our tumor response of VMAT alone was similar to theirs.

Table 4

Treatment outcomes of the Radiation Therapy Oncology Group 8502 regimen for head and neck cancer

Author	Year	Design	N	Population	SCC (%)	Age (years)	Systemic therapy (%)	RT technique		
2D-RT	3D-CRT	IMRT								
Paris	1992	Phase I–II	37	Incurable H&N tumors	79	66	0	100	0	0
Corry[a]	2005	Phase II	30	Incurable HNSCC	100	73	0	100	0	0
Chen	2008	R	23[b]	Metastatic HNSCC	100	70	0	20	65	15
Lok	2015	R	75	Incurable H&N tumors	55	76	29	0	45	55
Finnegan	2016	R	70	Stage III–IV HNSCC	100	66	56	0	49	51
Gamez	2017	R	21	Stage III–IV H&N tumors	NA	62	100	0	29	71
Our study		R	34	Incurable H&N tumors	82	81	0	0	0	100

Treatment cycle (%)					Outcome					Toxicity (%)	
1	2	3	4	5	TR (%)	SR (%)	OR (%)	OS (months)	PFS (months)	G2	G3
43		57	0	0	77	85	NA	4.5	NA	NA	NA
20	27	53	0	0	53	56	NA	5.7	3.1	37[c]	0
26		74	0	0	NA	NA	83	4	NA	NA	9
36	27	32	4	1	NA	NA	65	5.7	NA	28	5
24		76	0	0	NA	61	NA	3.9	3.4	20[d]	6

Abbreviations: R = retrospective study; H&N = head and neck; HNSCC = head and neck squamous cell carcinoma; SCC = squamous cell carcinoma; RT = radiotherapy; 2D-RT = two-dimensional radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; TR = tumor response; SR = symptom relief; OR = overall response; OS = overall survival; PFS = progression-free survival; G = grade.

[a] Corry et al. used a fraction size of 3.5 Gy

[b] Subset of 60 patients

[c] Salivary gland toxicity

[d] Mucositis

Author	Year	Design	N	Population	SCC (%)	Age (years)	Systemic therapy (%)	RT technique			
0	24	76	0	0	86	100	NA	7	4	35	0
18	15	68	0	0	85	77	94	5.7	4.4	12	0

Abbreviations: R = retrospective study; H&N = head and neck; HNSCC = head and neck squamous cell carcinoma; SCC = squamous cell carcinoma; RT = radiotherapy; 2D-RT = two-dimensional radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; TR = tumor response; SR = symptom relief; OR = overall response; OS = overall survival; PFS = progression-free survival; G = grade.

[a] Corry et al. used a fraction size of 3.5 Gy

[b] Subset of 60 patients

[c] Salivary gland toxicity

[d] Mucositis

The previous reported symptom response and overall response of the RTOG 8502 regimen with or without systemic therapy approximated 55–100% and 65–85%, respectively (8–11) (Table 4). Our results of symptom response were comparable to these results. Furtheremore, our results of overall response were superior to these results. RTOG 8502 regimen using VMAT provides appropriate treatment response without using systemic therapy: this treament strategy may improve or maintain patient QOL.

The previously reported median OS and PFS of the RTOG 8502 regimen with or without systemic therapy approximated 4–7 months and 3–4 months, respectively (8–11) (Table 4). Our results were similar with these results. Considering that the prognosis of patients with HNC who undergo non-curative treatment is poor with approximate survival time of 2–4 months (17, 18), palliative RT may contribute to a certin degree of prolonged survival. However, more than half of the patients die within 6 months even if they undergo palliative RT, including RTOG 8502 regimen (5, 6, 8–11). Therefore, a smaller number of fractions such as RTOG 8502 regimen is feasible for the palliative RT.

In our series, all patients who received 2 or more treatment cycles achieved overall response. Furthermore, completion of all 3 treatment cycles is significantly associated with better OS and PFS, which is consistent with previous reports (2, 11). Treatment with multiple cycles is recommended for better treatment response and/or survival.

The incidence of the Grade 2 and Grade 3 toxicities of patients with HNC treated with RTOG 8502 regimen was reported as approximately 20–40% and 0–10%, respectively (2, 9–11) (Table 4). Our results of toxicities were much lower than those of previous reports. The highly reduced toxicities in our patients may be attributed to several reasons. Firstly, we performed RT using VMAT, which provides excellent dose coverage to the target volume with a reduced dose to OARs (15). Secondly, we performed ART for every cycle. Just as the RTOG 8502 regimen achieved good tumor response, ART may avoid overdosing of OARs. Thirdly, we did not perform concurrent systemic therapy. We recommend the introduction of VMAT into palliative RT regimen with RTOG 8502 not only because of its excellent palliative response but because of the highly reduced toxicities.

On the other hand, this was a retrospective study based on a relatively small number of patients. The potential for selection bias exists, which may influence the results of the treatment outcomes and analysis. Further investigations are underway to address this issue.

Conclusions

The RTOG 8502 “QUAD shot” regimen using VMAT is effective for incurable HNC with highly reduced toxicities. Treatment with multiple cycles is recommended for better treatment response and/or survival.

Abbreviations

HNC
head and neck cancer
RT
radiotherapy
PS
performance status
QOL
quality of life
RTOG
Radiation Therapy Oncology Group
2D-RT
two-dimensional radiotherapy
3D-CRT
three-dimensional conformal radiotherapy
IMRT
intensity-modulated radiotherapy
CT
computed tomography
OAR
organs at risk
VMAT
volumetric modulated arc therapy
GTV
gross tumor volume
PTV
planning target volume
CBCT
cone-beam computed tomography
ART
adaptive radiothrapy
OS
overall survival
PFS
progression-free survival

Declarations

Ethics approval and consent to participate

This study received the full approval from the Institutional Research Ethics Board at Kumamoto University Hospital (No. 1830). The requirement for individual participant consent was waived by the research ethics board.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, but restrictions apply to the availability of the data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the Institutional Research Ethics Board at Kumamoto University Hospital.

Competing interest

The authors declare that they have no competing interests.

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None.

Author's contributions

RT developed the study design; collected, analyzed, and interpreted data; performed statistical analysis; and wrote the manuscript. TS developed the study design; analyzed and interpreted data; and performed statistical analysis. KY developed the study design and collected, analyzed, and interpreted data. TM, TW, and TM developed the study design and analyzed and interpreted data. RY, AH, and DM collected and interpreted data. YO, HN, and NO developed the study design and interpreted data. All authors have read and approved the final manuscript.

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Figures

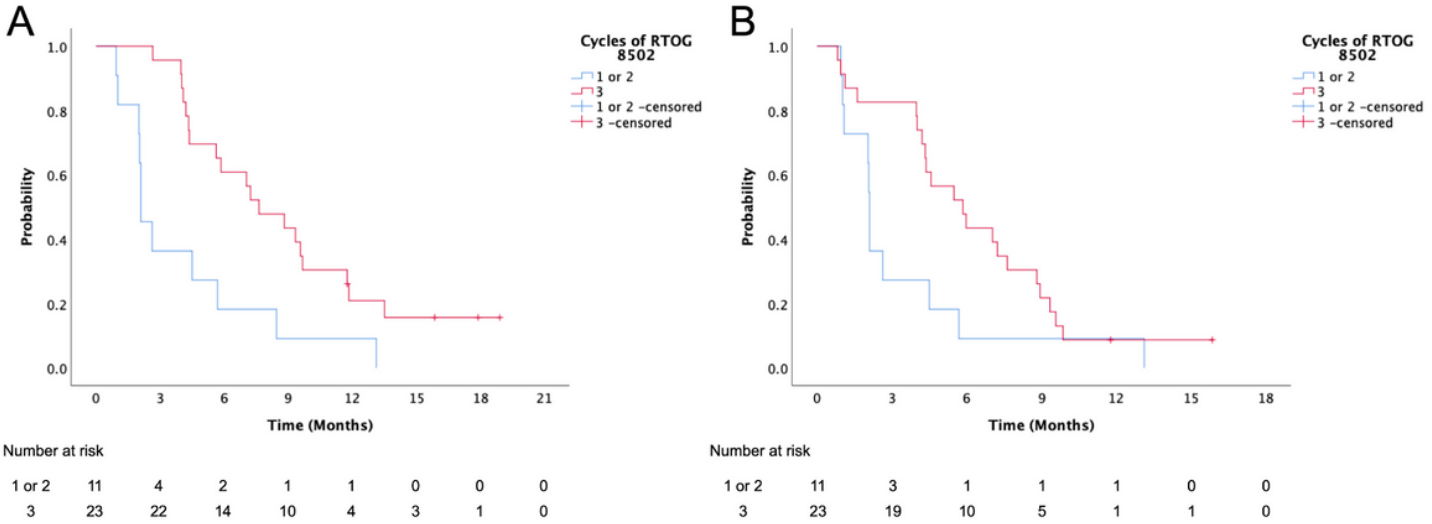

Figure 1

Overall (A) and progression-free (B) survival curves according to completed cycles of Radiation Therapy Oncology Group (RTOG) 8502 regimen