

Quality of life and quality-adjusted time without toxicity in palliatively treated head-and-neck cancer patients

Vijay Patil, Amit Joshi, Vanita Noronha, Atanu Bhattacharjee¹, Sachin Dhupal, M.V. Chandrakanth, Ashay Karpe, Vikas Talreja, Arun Chandrasekharan, Siddharth Turkar, Nikhil Pande, Anant Ramaswamy, Kumar Prabhash

Abstract

Background: Quality-adjusted time without toxicity (Q-TWiST) and quality of life (QOL) are indicators of benefit provided by different chemotherapy regimens. **Methods:** This was a prospective study, in which adult head-and-neck (H and N) cancer patients, treated with metronomic chemotherapy were enrolled. The Functional Assessment of Cancer Therapy-General H and N (FACT-G and H and N) version 4 pro formas were self-administered before the start of chemotherapy and then at 2, 4, and 6 months. FACT QOL and Q-TWiST analysis were then performed. **Results:** There was an improvement in the social well-being ($P = 0.370$), emotional well-being ($P = 0.000$), functional well-being ($P = 0.000$), H and N cancer subscale ($P = 0.001$), FACT H and N trial outcome index ($P = 0.000$), FACT G-total score ($P = 0.000$), and FACT H and N total score ($P = 0.000$) with palliative chemotherapy. The Q-TWiST value for a utility score of 0.25 for toxicity and relapse state was 145.93 days. **Conclusion:** Metronomic chemotherapy is associated with improvement in QOL and has a low duration of time spent in toxicity state.

Key words: FACT, head, neck cancers, palliative chemotherapy, quality-adjusted time without toxicity, quality of life

Introduction

Patients with recurrent or metastatic head-and-neck (H and N) cancers have a significant burden of symptoms and often suffer from concomitant disability arising out of disfigurement.^[1] Palliative chemotherapy is the mainstay of treatment in these settings with goals of improving survival and reducing symptoms, without worsening the quality of life (QOL).^[2,3] However, it is unknown to what extent it fulfills these outcomes. Maintenance or improvement of QOL, improvement in patient-reported symptoms, or a delay in deterioration in QOL are important end-points that seldom take the center stage in drug trials.^[4,5] QOL data are minimally reported in pivotal studies, and even when reported, a high proportion of missing data makes the interpretation difficult.

Patients treated with palliative chemotherapy have a modest lifespan.^[6,7] A balance needs to be struck between the benefits provided by chemotherapy and its adverse events. The use of chemotherapy protocols that lead to higher frequency and longer duration of adverse events, with marginal gains (days-to-weeks increment) in survival are rarely preferred by patients.^[5] Quality-adjusted time without toxicity (Q-TWiST) would probably be a better method to compare the benefit provided by different chemotherapy regimens.^[8] Certainly, there is limited data regarding Q-TWiST in H and N cancers.

Supportive-1 was a single arm, prospective observational study in H and N cancer patients undergoing palliative chemotherapy conducted at our tertiary cancer center.^[5] The key objectives of the study were to study the expectations and preferences of patients from chemotherapy, the baseline distress, and QOL. The results of baseline expectations and distress have already been published.^[5] The current manuscript focuses on the QOL and Q-TWiST analysis. The objectives of the current analysis were to report the temporal change in the various domains of QOL, time to first deterioration in trial outcome index (TOI), and Q-TWiST.

Methods

Participants

Adult, pathologically proven H and N cancer patients, with normal organ function, Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–2 requiring palliative chemotherapy, were invited for participation in this study. Patients with uncontrolled comorbidities, pregnant women, and those not willing to comply with study procedures were excluded from this study. The details of inclusion and exclusion criteria have already been published elsewhere.^[5]

Intervention

Two hundred patients who fulfilled the above-mentioned eligibility criteria were counselled regarding the prognosis, benefits, and risks of chemotherapy. After counseling, the distress, expectations, and preferences for chemotherapy and QOL were captured using the self-administered Functional Assessment of Cancer Therapy-Head and Neck (FACT-H and N) (version 4) QOL pro forma. Patients then received chemotherapy with or without cetuximab in accordance with the institutional protocols and logistics. Subsequently, these patients were followed up at 2 monthly intervals till death. FACT-H and N (version 4) QOL pro forma was again used to capture QOL at 2, 4 and 6 months.

Study oversight

The study was investigator initiated, approved by the institutional ethics committee (IEC-III) and received an intramural grant from Tata Memorial Centre. The study was registered with the CTRI (Clinical trial registry of India, CTRI/2015/11/006392). The patients were enrolled between December 1, 2015 and April 29, 2016. All patients were provided written informed consent before enrollment in the study. The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Patil V, Joshi A, Noronha V, Bhattacharjee A, Dhupal S, Chandrakanth MV, et al. Quality of life and quality-adjusted time without toxicity in palliatively treated head-and-neck cancer patients. South Asian J Cancer 2018;7:249-53.

Access this article online

Quick Response Code:



Website: www.sajc.org

DOI: 10.4103/sajc.sajc_233_17

Departments of Medical Oncology, ¹Statistics and Epidemiology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

Correspondence to: Dr. Kumar Prabhash, E-mail: kumarprabhastmh@gmail.com

Statistical analysis

The statistical analysis was done on SPSS version 16 (SPSS Inc., Chicago) and RStudio version 3.1.2 (RStudio, Inc., Boston, MA).

Quality of life analysis

Health-related QOL analysis was done according to the FACT group guidelines. The temporal relationship between different domain scores at baseline, 2, 4 and 6 months was compared using GLM repeated measures ANOVA. Listwise deletion of missing data was used for handling the missing values. The assumption of sphericity was tested using the Mauchly test of Sphericity. If the assumption was violated, then either the Greenhouse–Geisser epsilon or Huynh–Feldt epsilon was used for correction. For epsilon below 0.75, the Greenhouse–Geisser epsilon was used, while for epsilon above it, the Huynh–Feldt epsilon was used. $P = 0.05$ or below was considered significant for this analysis.

The mean scores at baseline and scores at 2, 4 and 6 months for FACT H and N total score, FACT G total score, and FACT H and N TOI were quantified using effect size measurement for two-dependent groups using Cohen's d , where d was the difference between the means ($M_T - M_B$) divided by the pooled standard deviation ($M_T - \text{Mean score at time T}$ and $M_B - \text{Mean score at baseline}$). The pooled standard deviation was calculated as the root mean square of the two standard deviations. The interpretation of effect size was done as "small," $d = 0.2$; "medium," $d = >0.2-0.5$; and "large," $d \geq 0.5-0.8$.

The time to deterioration of QOL (TDQ) was defined as time interval in days from the date of enrolment in the study to date of progression or date of death or date of deterioration of FACT H and N TOI by 6 units or greater, whichever was earlier. The change in FACT H and N TOI was calculated from the highest value of TOI. The median TDQ was estimated using Kaplan–Meier method.

The impact of pretreatment FACT H and N TOI on OS was explored using Cox regression analysis, with FACT H and N TOI used as a continuous variable. Exploratory analysis was then performed to identify the cutoff of value of FACT H and N TOI which would predict poor OS.

Quality-adjusted time without toxicity analysis

The overall survival (OS) was calculated as time interval in days from the date of enrolment in the study to the date of death. Patients who were alive at the time of analysis were censored for the analysis. Progression-free survival (PFS) was calculated as time interval in days from the date of enrolment in the study to the date of progression or death whichever was earlier. Patients who had not progressed at the time of analysis were censored for the analysis. TOX state was calculated as cumulative time interval in days spent in Grade 0–4 National Cancer Institute Common Terminology Criteria for Adverse events, between the date of enrolment to the date of progression. REL state was calculated as time interval in days from the date of progression to date of death. Time without symptoms or toxicities (TWiST) were calculated as time interval in days from the date of enrolment in the study to date of progression without Grade 3–4 CTCAE version 4.03 adverse events. The median and restricted mean value of OS, PFS, REL, TOX, and TWiST were estimated using the Kaplan–Meier method.

The mean QTWiST was calculated using the formula, Mean TWiST = Restricted mean PFS–Restricted mean TOX.

The mean QTWiST was calculated using the formula: Mean QTWiST = μ_{TOX} * Restricted mean TOX + Restricted mean TWiST+ μ_{REL} * Restricted mean REL.

μ_{TOX} and μ_{REL} are utility scores for TOX and REL health Status. As utility score values for H and N cancers are unknown, QTWiST scores were calculated using a permutation and combination of values from 0 to 1 in 0.25 increment for μ_{TOX} and μ_{REL} . Score of 1 denotes time of perfect health while a score of 0 denotes time period which is similar to death.

Results

Baseline details

The median age of the patients was 49.5 years (IQR 42.3–58.8 years). There were 175 men (87.5%) and 25 (12.5%) women. The ECOG PS was 0–1 in 181 patients and 2 in 19 patients. The primary site was oral cavity in 144 patients (72%) and other sites in 56 patients. Previous treatment was received by 143 patients (71.5%). Previous radiation exposure was present in 106 patients (53.0%) and previous platinum exposure was present in 78 patients (39.0%). The median time to failure post previous treatment was 3 months (IQR 0–7 months). The median monthly income was 57 USD (IQR 42.9–85.7 USD). All patients opted for oral metronomic therapy consisting of celecoxib 200 mg PO twice daily and methotrexate 15 mg/m² weekly.

QOI analysis

Compliance and reasons for noncompliance

FACT pro forma was filled by 196 patients (98%) at baseline, by 126 patients (63%) at 2 months, 87 patients (43.5%) at 4 months, and 51 patients (25.5%) at 6 months. The proportion of patients who had either died or were not in a condition to fill the pro forma were 31 patients (15.5%) at 2 months, 71 patients (35.5%) at 4 months, and 112 patients (56.0%) at 6 months. So among eligible patients, the compliance at baseline was 98% (196, $n = 200$), 76.4% (126, $n = 165$) at 2 months, 69.6% (87, $n = 125$) at 4 months, and 60.7% (51, $n = 84$) at 6 months.

Temporal comparison between all time points

Figures 1, 2 and Table 1 depict the temporal changes in various domains of QOL scores. Figures 1 and 2 depict the median scores with interquartile range and 95% confidence interval (CI) while Table 1 depicts the mean value with the standard

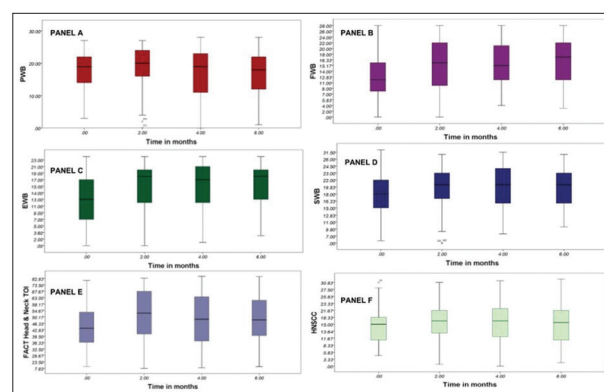


Figure 1: Temporal changes in different domains of the quality of life. Physical well-being, social/family well-being, emotional well-being, functional well-being, head-and-neck cancer subscale and Functional Assessment of Cancer Therapy-Head-and-Neck Trial outcome index

deviations. As can be seen from Figure 1 and Table 1, the scores of both mean and median have improved at 2 months in all domains and have then stabilized. A repeated-measures ANOVA, with Greenhouse–Geisser correction, indicated that the mean scores were different across all domains except the physical well-being domain [Table 1]. In the physical well-being domain too, there was a trend toward improvement.

Comparison between baseline value and scores at 2, 4, and 6 months time point

The comparison of FACT H and N TOI mean score at baseline with the mean score at 2 months (effect size-0.5055, large), 4 months (effect size-0.3323, medium), and 6 months (effect size-0.3080, medium) revealed improvement in these scores at these time intervals. Similar improvement was seen in the mean scores of FACT G total score and FACT H and N total score at 2, 4, and 6 months interval with respect to baseline mean scores [Table 2].

An improvement in FACT TOI of 6 units or more (considered as significant improvement in TOI) was seen in 50.8% of patients (64 patients, n = 126) at 2 months, 40.2% of patients (35, n = 87) at 4 months, and 39.2% of patients (20, n = 51) at 6 months. Deterioration in FACT TOI of 6 units or more was seen in 19.0% of patients (24 patient, n = 126) at 2 months, 27.6% of patients (24, n = 87) at 4 months, and 33.3% of patients (17, n = 51) at 6 months.

Time to deterioration in quality of life

The median follow-up was 366 days. Except for two patients, the remaining patients had an event occur for TDQ. The median TDQ was 71.0 days (95% CI 45.9 days–96.1 days) and 6 month TDQ was 16% (95% CI 10.9–21.1). Figure 3 depicts the TDQ curve.

Impact of baseline TOI on OS

Higher baseline value of FACT H and N TOI had a positive impact on OS (hazard ratio [HR]: 0.985, 95% CI 0.973–0.997, P = 0.015). On exploratory analysis, the cutoff value of 55 was able to discriminate patients with low OS. Patients with FACT H and N TOI value of 55 or more had a median OS of 223 days (95% CI 154.74–291.3) versus a

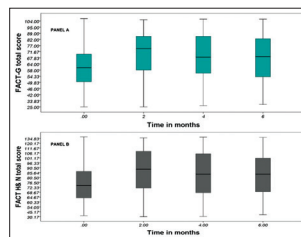


Figure 2: Temporal changes in different domains of Functional Assessment of Cancer Therapy- General total score and Functional Assessment of Cancer Therapy-head-and-neck total score

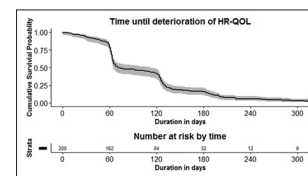


Figure 3: Time to deterioration in trial outcome index

Table 1: Mean scores of various domains at different time points

	Baseline	2 months	4 months	6 months	P
PWB	17.78 (5.19)	19.10 (5.82)	17.11 (9.49)	16.98 (6.60)	0.071
SWB	18.55 (7.89)	19.83 (5.19)	20.12 (5.38)	19.59 (4.96)	0.037
EWB	12.27 (5.80)	16.13 (5.59)	16.14 (5.95)	16.47 (5.20)	0.000
FWB	12.27 (5.90)	15.92 (7.17)	16.38 (15.17)	16.41 (6.48)	0.000
HN cancer subscale	15.01 (5.19)	17.22 (6.56)	16.98 (7.24)	16.12 (7.10)	0.001
FACT HN total score	75.78 (18.87)	88.64 (23.69)	86.37 (26.76)	85.34 (23.61)	0.000
FACT G total score	60.74 (15.71)	71.38 (18.40)	69.51 (20.80)	69.15 (18.50)	0.000
FACT HN TOI	45.07 (12.36)	52.59 (17.11)	50.39 (18.98)	49.69 (17.28)	0.000

The values in the bracket are the SD. SD: Standard deviation, PWB: Physical well-being, SWB: Social/family well-being, EWB: Emotional well-being, FWB: Functional well-being, FACT: Functional assessment of cancer therapy, TOI: Trial outcome index, HN: Head and neck

Table 2: Table depicting effect size of different scores at different time points with respect to respective baseline score

FACT HN TOI						
Time	FACT HN TOI mean score	SD of FACT HN TOI	Difference between mean FACT HN TOI and baseline score	SD pooled for getting effect size	Effect size	Cohen standard for effect size
Baseline	45.0725	12.32573	-	-	-	-
2 months	52.5936	17.11120	7.5211	14.87812	0.5055	Large
4 months	50.3896	18.97545	5.3171	15.99986	0.3323	Medium
6 months	49.6949	17.27708	4.6224	15.00701	0.3080	Medium
FACT-G total score						
Time	FACT-G mean score	SD of FACT-GI	Difference between mean FACT-G and baseline score	SD pooled for getting effect size	Effect size	Cohen standard for effect size
Baseline	60.7418	15.7078	-	-	-	-
2 months	71.3792	18.3980	10.6374	17.1059	0.6219	Large
4 months	69.5089	20.7974	8.7671	18.4291	0.4757	Medium
6 months	69.1467	18.4962	8.4049	17.1587	0.4898	Medium
FACT HN total score						
Time	FACT HN total mean score	SD of FACT HN total score	Difference between mean FACT HN total score and baseline score	SD pooled for getting effect size	Effect size	Cohen standard for effect size
Baseline	75.7565	18.8722	-	-	-	-
2 months	88.6388	23.6891	12.8832	21.4165	0.6056	Large
4 months	86.3720	26.7569	10.6155	23.1527	0.4585	Medium
6 months	85.3421	23.6051	9.5856	21.3701	0.4486	Medium

FACT: Functional assessment of cancer therapy, TOI: Trial outcome index, SD: Standard deviation, HN: Head and neck

median OS of 193 days (95% 168.5–217.5 days) in patients with score below 55 (HR: 1.648 95% CI 1.099–2.471, $P = 0.016$).

Quality-adjusted time without toxicity

The mean duration of PFS and OS was 130.2 days (95% CI 116.8–143.6 days) and 216.1 days (95% CI 198.7–233.5 days). The mean duration of time spent in TOX state was 7.6 days (95% CI 4.9–10.4 days), in REL state was 85.9 days (81.9–89.9 days) and in TWiST state was 122.6 days (95% CI 111.9–133.3 days). Figure 4 depicts the partitioned survival curve depicting all three health states. The results of threshold utility analysis are shown in Table 3.

Discussion

The current study confirms the importance of palliative chemotherapy in H and N cancer. Palliative chemotherapy leads to an improvement in all domains of QOL, except for physical well-being. The maximum improvement in most of these domains was at 2 months as implicated by the large effect size improvements seen in FACT H and N TOI score, FACT HNSCC total score, and FACT G score at 2 months. These improvements did remain stable for at least 6 months.

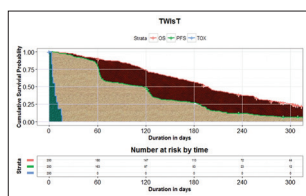


Figure 4: Partitioned curve depicting TWiST. REL: Time spent in relapse state, TOX: Time spent in toxicity (Grade 3–4), TWiST: Time spent without symptom or toxicity, OS: Overall survival, PFS: Progression-free survival

Table 3: Result of threshold utility analysis

TOX weight	REL weight	Q-TWiST
0	0	122.511
0.25	0	124.460
0.50	0	126.369
0.75	0	128.278
1.00	0	130.187
0	0.25	144.022
0.25	0.25	145.931
0.50	0.25	147.840
0.75	0.25	149.749
1.00	0.25	151.658
0	0.50	165.494
0.25	0.50	167.403
0.50	0.50	169.312
0.75	0.50	171.221
1.00	0.50	173.130
0	0.75	186.965
0.25	0.75	188.874
0.50	0.75	190.783
0.75	0.75	192.692
1.00	0.75	194.601
0	1.00	208.436
0.25	1.00	210.345
0.50	1.00	212.254
0.75	1.00	214.163
1.00	1.00	216.072

Q-TWiST: Quality-adjusted time without toxicity, TOX weight: The weight for utility coefficient of TOX, REL weight: The weight for utility coefficient of REL

The results in our study seem not in coherence with the QOL results reported from major palliative systemic therapy studies done in H and N cancer. The addition of cetuximab to standard palliative chemotherapy regimen of cisplatin-5 fluorouracil was associated with an improvement in OS.^[6] Similarly, improvement in OS with the metronomic combination of methotrexate and celecoxib was demonstrated by the author’s group when compared to single-agent cisplatin.^[7] However, in both these studies, the regimens associated with improvement in OS were unable to demonstrate improvement in QOL over the comparator regimen.^[9,10] Hence, it is incorrectly assumed that these palliative chemotherapy regimens which improve survival fail to demonstrate an improvement in QOL. The correct conclusion is that these regimens fail to improve QOL over their comparator arms. Data from a study done by Stewart *et al.* is inline with the above conclusion. In this study, gefitinib was compared with methotrexate, and there was no difference in QOL scores between the two arms but QOL score and symptom improvement scores improved from baseline with treatment.^[11] Even in the EXTREME study, the use of cetuximab led to an improvement in global health score and an improvement in certain symptom scores (pain, swallowing, speech problems, and social eating) after three cycles.^[9] Similar improvements in symptom scales with metronomic chemotherapy (pain) were reported by us.^[10] Even in the LUX H and N-1 study, use of afatinib delayed deterioration of global health status and improved swallowing and pain versus methotrexate.^[12]

Interpretation of the quality of data needs to be done taking into consideration the methodology used for handling missing data and the measure used to capture it. The missing data could be because of two reasons; missing at random or nonrandom missing.^[13] The nonrandom phenomenon in H and N cancers in the palliative setting is likely due to death or refusal to fill QOL due to progression of disease. Complex statistical methods have been designed that can handle such missing data. However, we feel that the reason for the missing data should guide the use of simple clinically relevant methods for analysis. For example, in the current study, missing data was ignored while doing the GLM ANOVA analysis and hence the data shown in Table 1 and Figure 2 show that there was improvement in QOL domains at 2 months and it persisted till 6 months. This step was taken as the missing data was predominantly patients who had either progressed or died. The idea of this analysis was to know the state of QOL in patients benefiting from chemotherapy (i.e., not progressing). This, however, failed to show the impact chemotherapy had on QOL and so the effect size analysis was done. The effect size analysis implied that the improvement in QOL with chemotherapy is time dependent and it is maximum at 2 months. This has implications in planning studies with QOL as the primary end-point. However, the above-described method of ignoring missing data has an important fallacy when comparing multiple arms. Consider a study with two arms, in which, one arm has a low PFS and the other arm has a high PFS. QOL data analysis, ignoring the missing data might show that both arms have similar QOL or a higher QOL in one arm. However, interpretation of such data in isolation becomes difficult. Conducting a TDQ analysis where progression, death, and deterioration in QOL are taken as events, might be a better method. In this study, the median TDQ in H-and-N cancer was 70 days.

EORTC and FACT QOL pro formas are the commonly used tools for measurement of QOL.^[12] Nearly, all major palliative chemotherapy studies done in H and N cancer have utilized the EORTC scale. FACIT scales have more reliability, validity, and responsiveness.^[14-16] It is a recommended scale for measurement of core domains of health-related QOL, especially when focus is on family relationships, social support, and social activities.^[14] Oral cancers contribute to 30% of cancer burden in the author's country and 70% of H-and-N cancer burden. Owing to the physical disfigurement, these cancers are associated with social isolation and hence the authors selected FACT H and N QOL pro formas for the current study.^[17] The study generated the data regarding values of TOI and overall score (FACT G total score and FACT HN total score) in palliative chemotherapy setting. This data would enable investigators to plan studies to test newer interventions. One of the advantages of FACT is that it has multiple composite scores which take into account multiple domains such as physical, social, emotional, functional, and H and N symptom scales into account. FACT H and N TOI is one such score. Data regarding prognostic impact of baseline TOI in H and N cancer with palliative chemotherapy were published by Urba *et al.*^[18] Our study also confirmed the importance of baseline TOI in predicting OS. Such composites scores analysis is probably better than having individual symptom analysis and global QOL analysis, the results of which are dependent on the answer to a single question.

Data regarding TWiST analysis have never been reported in palliative settings in H-and-N cancer. The patients in this study had received metronomic chemotherapy consisting of metronomic dose of methotrexate and celecoxib, which is associated with lower incidence of adverse events. Even the recovery of adverse events is relatively faster with metronomic therapy than maximum-tolerated chemotherapy. This is reflected in the mean duration of TOX health state, which was 7.6 days. The utility analysis was done for combination of values between 0 and 1 for different utility scores as the data regarding the utility score value for TOX and REL state is not available for H and N cancer patients. The data confirm the excellent safety profile of metronomic and the relative higher amount time spent in TWiST as the toxicities are negligible when metronomic chemotherapy is administered.

Conclusion

Metronomic chemotherapy was associated with improvement in QOL. It is also associated with less time spent in TOX state.

Financial support and sponsorship

This study was financially supported by TRAC (Intramural grant from TMC).

Conflicts of interest

There are no conflicts of interest.

References

- Gandhi AK, Roy S, Thakar A, Sharma A, Mohanti BK. Symptom burden and quality of life in advanced head and neck cancer patients: AIIMS study of 100 patients. *Indian J Palliat Care* 2014;20:189-93.
- Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. *Ann Oncol* 2010;21 Suppl 7:vii252-61.
- Parikh P, Patil V, Agarwal JP, Chaturvedi P, Vaidya A, Rathod S, *et al.* Guidelines for treatment of recurrent or metastatic head and neck cancer. *Indian J Cancer* 2014;51:89-94.
- Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2006;24:2644-52.
- Patil V, Joshi A, Noronha V, Deodhar J, Bhattacharjee A, Dhumal S, *et al.* Expectations and preferences for palliative chemotherapy in head and neck cancers patients. *Oral Oncol* 2016;63:10-5.
- Vermorken JB, Mesia R, Rivera F, Remenar E, Kaweckí A, Rottey S, *et al.* Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116-27.
- Patil VM, Noronha V, Joshi A, Muddu VK, Dhumal S, Bhosale B, *et al.* A prospective randomized phase II study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck. *Oral Oncol* 2015;51:279-86.
- Tate WR, Skrepnek GH. Quality-adjusted time without symptoms or toxicity (Q-TWiST): Patient-reported outcome or mathematical model? A systematic review in cancer. *Psychooncology* 2015;24:253-61.
- Mesía R, Rivera F, Kaweckí A, Rottey S, Hitt R, Kienzer H, *et al.* Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Ann Oncol* 2010;21:1967-73.
- Noronha V, Joshi A, Marfatia S, Patil V, Juvekar S, Arya S, *et al.* Health-related quality of life in patients with metastatic, relapsed, or inoperable squamous cell carcinoma of the head and neck in India. *Support Care Cancer* 2016;24:1595-602.
- Stewart JS, Cohen EE, Licitra L, Van Herpen CM, Khorprasert C, Soulieres D, *et al.* Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol* 2009;27:1864-71.
- Licitra L, Mesía R, Keilholz U. Individualised quality of life as a measure to guide treatment choices in squamous cell carcinoma of the head and neck. *Oral Oncol* 2016;52:18-23.
- Ibrahim JG, Chu H, Chen MH. Missing data in clinical studies: Issues and methods. *J Clin Oncol* 2012;30:3297-303.
- Luckett T, King MT, Butow PN, Oguchi M, Rankin N, Price MA, *et al.* Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: Issues, evidence and recommendations. *Ann Oncol* 2011;22:2179-90.
- Cheung YB, Goh C, Thumboo J, Khoo KS, Wee J. Variability and sample size requirements of quality-of-life measures: A randomized study of three major questionnaires. *J Clin Oncol* 2005;23:4936-44.
- Kemmler G, Holzner B, Kopp M, Dünser M, Margreiter R, Greil R, *et al.* Comparison of two quality-of-life instruments for cancer patients: The functional assessment of cancer therapy-general and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30. *J Clin Oncol* 1999;17:2932-40.
- Reich M, Leemans CR, Vermorken JB, Bernier J, Licitra L, Parmar S, *et al.* Best practices in the management of the psycho-oncologic aspects of head and neck cancer patients: Recommendations from the European Head and Neck Cancer Society make Sense Campaign. *Ann Oncol* 2014;25:2115-24.
- Urba S, Gatz J, Shen W, Hossain A, Winfree K, Koustenis A, *et al.* Quality of life scores as prognostic factors of overall survival in advanced head and neck cancer: Analysis of a phase III randomized trial of pemetrexed plus cisplatin versus cisplatin monotherapy. *Oral Oncol* 2012;48:723-9.