Tracking the dropout patients of neoadjuvant chemotherapy with locally advanced oral cavity cancer

Jin-Ye Fu*, Chen-Ping Zhang and Zhi-Yuan Zhang*

Abstract

Background: Patients with locally advanced oral cavity cancer sometimes stopped treatment after neoadjuvant chemotherapy. There are no guidelines of the management for these patients. Before designing clinical trials, we conducted this study to investigate their characteristics, reasons of dropout, and the follow-up information.

Methods: Medical records were consecutively reviewed of patients with locally advanced oral cavity cancer who underwent neoadjuvant chemotherapy from Jan 2017 to Dec 2019. Variables were compared between patients stopped treating after chemotherapy and completed treatments by student t-test and Chi-square test. Logistic regression model was used to calculate the odd rations of potential predictors of dropout. The dropout patients were followed up for reasons and results of their decision.

Results: A total of 171 patients were included with 23 not undergoing surgery after chemotherapy. The odd ratios of age over 65 and single marital status were 3.11 (95% CI: 1.1, 8.7) and 4.935 (95% CI: 1.5, 16.1), respectively, for the dropout. The median survival of patients without surgery was 7.4 months. Believing that chemotherapy would be effective and being afraid of the consequence of surgery were the main reasons of refusing surgery.

Conclusions: The prognosis was poor of these dropout patients. Symptom relief and fear of surgery were the reasons of dropout. Age and marital status affected their decision. Clinical trials are needed to be designed for these patients.

Keywords: Drop-out patients, Neoadjuvant chemotherapy, Oral cancer, Median survival, Decision making, Nonsurgical treatment

Introduction

Locally advanced oral cavity cancer is highly morbid and life threatening. The conventional treatment modality is radical resection with free flap reconstruction, followed by radiotherapy or chemoradiotherapy [1]. However, the probability of cure is still low [2, 3]. Neoadjuvant chemotherapy, followed by radical surgery, may be a choice for these patients. Its advantages include downsizing the primary tumor to improve locoregional control and reducing the incidence of distant metastasis by targeting circulating tumor cells. TPF regimen, that is taxane/ platinum/ 5-fluorouracil triplets, has obtained promising results [4–8]. Thus, this strategy has been applied in clinical practice for selected patients with locally advanced oral cavity cancer in our department.

Along with the application of neoadjuvant chemotherapy, there has created a population of dropout patients, who refused to follow the protocol of undergoing
surgery after taking the medicine. They had initially planned to treat the disease with radical curative management but did not adhere to the procedure after chemotherapy. There were no guidelines on how to treat this group of patients. In addition, because of drop out, their follow-up information was usually ignored. The reasons and results of these patients have little been reported in literatures. Understanding why they did not maintain in treatment and showing their follow up information would improve the clinical work of treating oral cavity cancer patients. And, for the planning of clinical trials, this entity may be a unique one to study for.

In this study, we focused on the population who withdrew from neoadjuvant chemotherapy in treatment for locally advanced oral cavity cancer and exhibited the patients’ follow up information, including the reasons and results of their decision.

Materials and methods

Ethics
The ethical approval was waived by the institutional review board of our hospital in view of the retrospective nature of the study and all the procedures being performed were in conformity with the provisions of the Declaration of Helsinki.

Data acquisition
We consecutively reviewed medical documents of patients with locally advanced oral cavity cancer who had undergone neoadjuvant chemotherapy of TPF regimen in our department from Jan 2017 to Dec 2019. The inclusion criteria were patients with newly diagnosed and histopathologically proved squamous cell carcinoma of oral cavity, which is of tongue, buccal, gingiva, palate, and floor of mouth. The tumor stages were clinically classified as T2 to T4a with N1 or N2, or clinical stage of N0 with T3 or T4a, according to the Cancer Staging Manual of American Joint Committee on Cancer [9]. Radical surgery was planned to be performed after neoadjuvant chemotherapy at the beginning of treatment. The treatment plan was recorded in medical history document. The exclusion criteria were patients with distant metastasis, serious concomitant diseases, or the follow up information was not available. Patients who refused to have radical surgery before chemotherapy were not included in this study.

The retrieved information included the demographic characteristics, the chemotherapy regimen, response and adverse of chemotherapy, and the surgical performance. Patients without surgical records were followed up by telephone to themselves. If there was no answer from the patients, we called the patients’ immediate families, namely parents, children, or spouse, who lived together with the patients and took care of them during the treatment. The phone calls first confirmed whether the surgery had been done. If it was confirmed that the patients had not undergone surgery, open questions would be asked, including reasons of absence of surgery, treatment after neoadjuvant chemotherapy, reasons of taking such management, changes of patients’ symptoms, and the final results of the patients. The persons who answered the phone were encouraged to describe as detailed as possible. The relationship of the person who answered the phone with the patient and the date of the call were recorded. The data in the study was derived from these telephone communications, including ascertaining the patient’s reasons for withdrawn and changes of symptoms.

Definitions of response to chemotherapy were conformed to the Response Evaluation Criteria in Solid Tumors version 1.1 [10]. In brief, tumor response to chemotherapy was classified as CR (complete remission, complete disappearance of all tumor lesions), PR (partial response, tumor residual with reduction of the largest dimension ≥30%), PD (progressive disease, enlargement of tumor size ≥20% or new tumor lesion manifestation), and SD (stable disease, tumor dimension changes between PR and PD and no new lesions).

Adverse events of TPF regimen were recorded of reduced white blood cell counting and frequency of vomiting in medical records. They were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [11].

Statistical analysis
Data analyses were performed using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL). For continuous variables, the mean, median, and standard deviation were calculated. Survival time in months for dropout patients was measured from the date of first dose of chemotherapy given to the date of death. Variables of smoking and drinking habits were only compared in men patients, because few women patients reported having these habits. Independent-sample t-test was used for continuous data comparison. Chi-squared test or Fisher’s exact test were used for comparisons of categorical data between patients with and without surgery. P-values were two-sided and smaller than 0.05 were considered statistically significant.

Multivariable analysis was done by logistic regression model to obtain odds ratios (OR) and 95% confidence interval (95%CI) of the baseline characters for dropout group compared to treatment completion group. Factors included in the regression model as potential predictors were sex (men, women), age (≤65, >65 years), marital
status (married, never married/divorced/widowed), educational level (college and above, under college), and tumor stage (Stage III, IV).

Results
Baseline characteristics of patients
A total of 171 patients were eligible during the study period, including 148 undergoing surgery and 23 without surgery after chemotherapy. The baseline characteristics are shown in Table 1. The dropout group had a higher proportion of men and elder patients than the treatment completion group but without significance. There were more single patients, which included never married, divorced, or widowed, in the dropout group and significantly so. Tumor staged T4a accounted for more in the dropout group. Other baseline characteristics were not different.

When combined in the regression model, variables of age over 65 years (OR = 3.110, 95%CI: 1.108, 8.733) and single marital status (OR = 4.935, 95%CI: 1.511, 16.121) were significant as a risk factor of dropout among the studied patients.

Table 2 shows the response and the adverse events of neoadjuvant chemotherapy in the two groups. Patients who dropped out after chemotherapy reported vomiting more severely. Response to chemotherapy and white blood cell decrease were not different between the groups.

Follow-up information of the dropout patients
Among the 23 dropout patients, most had passed away when we telephoned. Only one patient had been alive for over 2 years when data censored. So, the information was mostly obtained from patients’ family members. The median survival time of the 22 patients were 7.4 months, ranging from 2 to 17 months. The reasons for patients refused to undergo surgery were summarized as: 1) symptoms relieved and thought that the chemotherapy would be effective, in 19 patients; 2) fearing of the consequences of surgery, that is the loss of oral function and disfigurement of facial appearance. This fear of surgery may be more obvious in oral cancer patients than in patients with cancers of other sites. The TPF regimen had been reported a high response rate between 50 and 80% [4–8]. Though, these studies were conducted in preoperative medication, for the dropout patients, the relief of symptoms made them believed that the medicine would work for their disease and refused to accept the following surgery.

Surgical-based treatment is still the mainstay for locally advanced oral cavity cancer. However, the consequent loss of oral function is unavoidable and overall survival remained poor. Alternative therapies are appealed for by the patients who refused to undertake surgery. Definitive chemoradiation has been long explored. Its overall survival rate has been reported from 15 to 63% [12–17]. The discrepancy in the overall survival rate may be resulted from the patient inclusion criteria and the use of different radiation techniques or chemomedicines. Foster and his colleagues [18] reported a favorable outcome of definitive chemoradiotherapy with durable toxicity and considered it as a viable and feasible strategy for patients with locally advanced oral cavity cancer who did not want to undertake surgery.

There is a current interest in incorporating target medicines or immunotherapy in treatment for advanced oral cancers. The addition of cetuximab, an epidermal growth factor receptor monoclonal antibody, to the traditional platinum/5-fluorouracil regimen has shown a promising result [19, 20]. Its concomitant use with definitive radiotherapy also improved the locoregional control [21].

Nonsurgical treatment option
Most patients in the dropout group in our study believed that chemotherapy would be effective for their disease, because their symptoms relieved after using the medicine. Patients with oral cavity cancer were often scared of the radical performance because of the consequent loss of oral function and disfigurement of facial appearance. This fear of surgery may be more obvious in oral cancer patients than in patients with cancers of other sites. The TPF regimen had been reported a high response rate between 50 and 80% [4–8]. Though, these studies were conducted in preoperative medication, for the dropout patients, the relief of symptoms made them believed that the medicine would work for their disease and refused to accept the following surgery.

Surgical-based treatment is still the mainstay for locally advanced oral cavity cancer. However, the consequent loss of oral function is unavoidable and overall survival remained poor. Alternative therapies are appealed for by the patients who refused to undertake surgery. Definitive chemoradiation has been long explored. Its overall survival rate has been reported from 15 to 63% [12–17]. The discrepancy in the overall survival rate may be resulted from the patient inclusion criteria and the use of different radiation techniques or chemomedicines. Foster and his colleagues [18] reported a favorable outcome of definitive chemoradiotherapy with durable toxicity and considered it as a viable and feasible strategy for patients with locally advanced oral cavity cancer who did not want to undertake surgery.

There is a current interest in incorporating target medicines or immunotherapy in treatment for advanced oral cancers. The addition of cetuximab, an epidermal growth factor receptor monoclonal antibody, to the traditional platinum/5-fluorouracil regimen has shown a promising result [19, 20]. Its concomitant use with definitive radiotherapy also improved the locoregional control [21].
Another milestone of nonsurgical treatment option for oral cavity cancer is the advent of the immune modulating antibodies, such as programmed cell death protein-1 antibodies and its ligand [22, 23]. Though these studies are still pilot and inconclusive, the results are expected.

**Table 1** Baseline characteristics of patients with neoadjuvant chemotherapy for locally advanced oral cavity cancer

| Characteristics                     | Undergoing surgery (N = 148) | Without surgery (N = 23) | Statistical value a | P-value |
|-------------------------------------|------------------------------|--------------------------|---------------------|---------|
| Age, year                           |                              |                          |                     |         |
| Mean ± SD                           | 56.7 ± 10.8                  | 59.8 ± 10.0              | 1.285               | 0.201   |
| Median (range)                      | 59 (29–73)                   | 63 (40–72)               |                     |         |
| Gender, n                           |                              |                          |                     |         |
| Male                                | 109                          | 20                       |                     |         |
| Female                              | 39                           | 3                        |                     |         |
| Marital status, n                   |                              |                          |                     |         |
| Married                             | 136                          | 17                       | 1.903               | 0.168   |
| Unmarried/ Divorce/ Widowed         | 12                           | 6                        |                     |         |
| Smoking in men, n                   |                              |                          |                     |         |
| Current smoker                      | 85                           | 12                       | 2.045               | 0.153   |
| Former smoker/Nonsmoker             | 24                           | 8                        |                     |         |
| Alcohol drinking in men, n          |                              |                          |                     |         |
| Light                               | 68                           | 10                       | 1.150               | 0.284   |
| Heavy                               | 41                           | 10                       |                     |         |
| Educational level, n                |                              |                          |                     |         |
| College or above                    | 49                           | 8                        | 0.025               | 0.874   |
| Below college                       | 99                           | 15                       |                     |         |
| Primary site, n                     |                              |                          |                     |         |
| Tongue                              | 63                           | 14                       | 3.745               | 0.404   |
| Bucca                               | 30                           | 2                        |                     |         |
| Gingiva                             | 23                           | 2                        |                     |         |
| Palate                              | 4                            | 1                        |                     |         |
| Floor of mouth                      | 28                           | 4                        |                     |         |
| HPV status, n                       |                              |                          |                     |         |
| Negative                            | 98                           | 16                       | 0.100               | 0.751   |
| Positive                            | 50                           | 7                        |                     |         |
| T classification, n                 |                              |                          |                     |         |
| 2/3                                 | 103                          | 11                       | 4.245               | 0.039   |
| 4a                                  | 45                           | 12                       |                     |         |
| N classification, n                 |                              |                          |                     |         |
| 0                                   | 32                           | 3                        | 1.330               | 0.539   |
| 1                                   | 51                           | 7                        |                     |         |
| 2                                   | 65                           | 13                       |                     |         |
| Clinical stage, n                   |                              |                          |                     |         |
| III                                 | 65                           | 7                        | 1.485               | 0.223   |
| N4                                  | 83                           | 16                       |                     |         |

SD standard deviation, HPV human papilloma virus

*a The Statistical values referred to the t-value for continuous variables and the χ²-value for categorical variables

**Age and marital status in cancer treatment**

Age and marital status may affect patients’ decision making in cancer treatment. Our study showed that patients with age over 65 years or with single marital status were at risk of abandon surgery after neoadjuvant.
chemotherapy. Elder patients may have more reasons than the young that made them unable to retain in the long-term treatment duration. Literatures have reported the reasons, such as comorbid conditions or progression of disease [24, 25]. However, be afraid of loss function and unable to take care of themselves were also the reasons for the elder to dropout. Among the 23 patients who did not complete the prescribed treatment, over half reported their worry of caring themselves after chemotherapy. Oral cavity cancer can have a negative impact on patients’ daily life. Chewing or swallowing becomes a problem that troubles the patients in feeding themselves. They may experience slurred speech and difficulties in communicating with others. Also the expected alteration of facial appearance will make them psychologically depressed [26–28]. In addition, chemotherapy is considered to be one of strong stressors to older patients [29, 30].

Marital status to the compliance of cancer treatment was inconclusive. However, single persons, which include never married, divorced, or widowed, had reported a poorer survival than the married ones [31–33]. One reason was that they were more likely to be insufficiently treated; while, married persons more frequently received definitive or potentially curative treatment [34–36]. This might be affected by social support, psychological problem, or economic aspects, which were partially mediated via marital status, on deciding the choice of cancer treatment modality. One study had showed higher proportion of receiving surgery for cancer in married persons than in the unmarried [37]. It was owing to the at-home day-to-day support that made the patients willing to take on the risks associated with surgery. In our study, the proportion of single person was higher in the dropout group. Their reasons of dropout included nobody to discuss with and lack of information on treatment.

Communications between patients and clinicians
The main reason of withdrawn in this study may be the insufficient information patients obtained. From the telephone with family members, it indicated that patients believed chemotherapy being effective mostly because of symptom relief. At the same time, they saw that radical surgery would cause serious functional loss. However, sometimes patients’ understanding of disease was one-sided. Communication between patients and clinicians needs to be improved in clinical practice, including survival probability, toxicity of treatment, time to recurrence, treatment burden, and also the health-related quality of life, from the initial stage of consultation, treatment decision, management duration, to rehabilitation stage. It may also help patient understand the disease that let the patients access to other patients at the time of decision making. In any case, we should understand, accept, and respect the patients’ decision and do our best to support them.

There were some limitations of the study. First is its retrospective nature. The reasons of dropout were mainly based on recall of the patients’ families, because most of the dropout patients were no longer alive when we telephoned. It may create recollection bias. Other variables, such as depression, anxiety, distress, and personality, could affect the patients’ decision but had not been recorded in this study. There was a T2N1 patient in the study group which was not normally suited to neoadjuvant chemotherapy. The study had a small number of dropout patients, which is not strong enough for statistical power. However, this entity is not common and has little been mentioned previously. We presented the relative factors of absence of surgery and the follow-up information of these patients for further study.

Table 2 Response and adverse of neoadjuvant chemotherapy among patients with locally advanced oral cavity cancer

|                | Undergoing surgery (N = 148) | Without surgery (N = 23) | X² value | P - value |
|----------------|-----------------------------|--------------------------|----------|-----------|
| Response a     |                             |                          | 0.401    | 0.859     |
| PR             | 81                          | 14                       |          |           |
| SD             | 60                          | 8                        |          |           |
| PD             | 7                           | 1                        |          |           |
| Adverse events b |                            |                          |          |           |
| WBC decreased  |                             |                          | 0.254    | 0.614     |
| Grade 0/1      | 137                         | 20                       |          |           |
| Grade 2/3      | 11                          | 3                        |          |           |
| Vomiting       |                             |                          | 9.082    | 0.003     |
| Grade 0/1      | 143                         | 18                       |          |           |
| Grade 2/3      | 5                           | 5                        |          |           |

a The response definitions were classified according to the Response Evaluation Criteria in Solid Tumors version 1.1
b The adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
Conclusion
In our study, the survival of the dropout patients was poor except one still alive at last follow-up. Most patients died of dyspnea, tumor bleeding, aspiration, or systemic failure. Thus, the dropout patients formed a special entity and urged to be studied for. The main reasons of dropout were the thinking that the medicine would be effective for the disease and the fearing of the consequence of radical surgery. Clinical trials are needed to be designed for these patients who had undergone neoadjuvant chemotherapy but refused the following surgery.

Acknowledgements
The authors wish to thank Mr. Wen Tao Shi for his statistical support, Ms. Cen Chen for helping in information collection, and the patients’ families for their answering the phone calls and replying to the questions. Also, we wish to thank the general support by Shanghai Clinical Research Center for Oral Diseases (19WC190600) and Shanghai Municipal Key Clinical Specialty (shlszdck01601).

Authors’ contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jin-Ye Fu. The first draft of the manuscript was written by Jin-Ye Fu. Chen-Ping Zhang and Zhi-Yuan Zhang reviewed and edited the previous versions of the manuscript. All authors read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
The data and materials that support the findings of this study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The ethical approval was waived by the institutional review board of Shanghai Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine in view of the retrospective nature of the study. All the procedures performed in the study were in conformity with the provisions of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The consent to participate is also waived by the institutional review board of Shanghai Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflict of interest.

Received: 20 February 2021 Accepted: 24 May 2021
Published online: 03 June 2021

References
1. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN Guidelines) head and neck cancers version 2. 2020;2020. Available from https://www.nccn.org/professionals/physician_ gl/pdf/head-and-neck.pdf. Accessed 10 Feb 2021.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.
3. Kim D, Li R. Contemporary treatment of locally advanced oral cancer. Curr Treat Options in Oncol. 2019;20(4):32. https://doi.org/10.1007/s11864-019-0631-8.
4. Inheister J, Schmalenberg H, Dietz A, Rotter N, Maschmeyer G, Jungelhüsling R, et al. A two-arm multicenter phase II trial of one cycle chemoselection split-dose docetaxel, cisplatin and 5-fluorouracil (TPF) induction chemotherapy before two cycles of split TPF followed by curative surgery combined with postoperative radiotherapy in patients with locally advanced oral and oropharyngeal squamous cell cancer (TSC01). Ann Oncol. 2017;28(8):1917–22. https://doi.org/10.1093/annonc/mdx202.
5. Patil VM, Prabhash K, Noronha V, Joshi A, Mudru V, Dhunmal S, et al. Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers. Oral Oncol. 2014;50(10):1000–4. https://doi.org/10.1016/joraloncology.2014.07.015.
6. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007;357(17):1705–15. https://doi.org/10.1056/NEJMoa070956.
7. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007;357(17):1695–704. https://doi.org/10.1056/NEJMoa071028.
8. Zhong LP, Zhang CP, Ren GX, Guo W, William WN Jr, Sun J, et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. J Clin Oncol. 2013;31(6):744–51. https://doi.org/10.1200/JCO.2012.43.8820.
9. Edge SB, Byrd DR, Compton CC, et al. Lip and Oral Cavity. In: AJCC Cancer Staging Manual (7th edn.). New York: Springer; 2010. p. 29–40.
10. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228–47. https://doi.org/10.1016/j.ejca.2008.10.026.
11. National Cancer Institute (NCI). U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v5.0; 2017. Available from https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Accessed 10 Feb 2021.
12. Cohen BE, Banu J, Luo D, et al. Efficacy and safety of treating T4 oral cavity tumors with primary chemoradiotherapy. Head Neck. 2009;31(8):1013–21. https://doi.org/10.1002/hed.21062.
13. Pederson AW, Salama JK, Witt ME, Stenson KM, Blair EA, Vokes EE, et al. Concurrent chemoradiotherapy and intensity-modulated radiotherapy for organ preservation of locoregionally advanced oral cancer. Am J Clin Oncol. 2011;34(4):356–61. https://doi.org/10.1097/COC.0b013e3181e8420b.
14. Scher ED, Romesser PB, Chen C, Ho F, Wuu Y, Sherman EJ, et al. Definitive chemoradiation for primary oral carcinoma: a single institution experience. Oral Oncol. 2015;51(7):709–15. https://doi.org/10.1016/j.oraloncology.2015.04.007.
15. Soo KC, Tan EH, Wee J, Lim D, Tai BC, Khoo ML, et al. Surgery and adjuvant radiotherapy vs concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison. Br J Cancer. 2005;93(3):279–86. https://doi.org/10.1038/sj.bjc.6602696.
16. Spiotto MT, Jefferson G, Wenig B, Markiewicz M, Weichselbaum RR, Kosh Y. Differences in survival with surgery and postoperative radiotherapy compared with definitive chemoradiotherapy for oral cavity cancer: a National Cancer Database analysis. JAMA Otolaryngol Head Neck Surg. 2017;143(7):691–8. https://doi.org/10.1001/jamaoto.2017.0012.
17. Stenson KM, Kunnavakkam R, Cohen EE, et al. Chemoradiation for patients with advanced oral cavity cancer. Laryngoscope. 2010;120:709–15. https://doi.org/10.1002/lary.21062.
18. Foster CC, Meketek JM, Brisson RJ, Selwett TY, Cohen EEW, Stenson KM, et al. Definitive chemoradiation for locally-advanced oral cancer: a 20-year experience. Oral Oncol. 2018;80:16–22. https://doi.org/10.1016/j.oraloncology.2018.03.008.
19. Mesia R, Rivera F, Kawecki A, Rottey S, Hirtt R, Kenzer H, et al. Quality of life of patients receiving platinum-based chemoradiotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 2010;21(10):1967–73. https://doi.org/10.1093/annonc/mdq077.
20. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359(1):1116–27. https://doi.org/10.1056/NEJMoa0802656.
21. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567–78. https://doi.org/10.1056/NEJMoa053422.

22. Ferris RL, Blumenschein Jr, Fayette J, et al. Nivolumab for recurrent squamous cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–67. https://doi.org/10.1056/NEJMoa1602252.

23. Burtness B, Harrington KJ, Greil R, Souléères D, Tahara M, de Castro G Jr, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394(10212):1915–28. https://doi.org/10.1016/S0140-6736(19)32591-7.

24. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341(27):2061–7. https://doi.org/10.1056/NEJM199912303412706.

25. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003;21(7):1383–9. https://doi.org/10.1200/JCO.2003.08.010.

26. Oskam IM, Verdonck-de Leeuw IM, Aaronson NK, Witte BI, de Bree R, doornaert P, et al. Prospective evaluation of health-related quality of life in long-term oral and oropharyngeal cancer survivors and the perceived need for supportive care. Oral Oncol. 2013;49(5):443–8. https://doi.org/10.1016/j.oraloncology.2012.12.005.

27. So WK, Chan RJ, Chan DN, et al. Quality-of-life among head and neck cancer survivors at one year after treatment -- a systematic review. Eur J Cancer. 2012;48(15):2391–408. https://doi.org/10.1016/j.ejca.2012.04.005.

28. Valdez JA, Brennan MT. Impact of Oral Cancer on quality of life. Dent Clin N Am. 2018;62(1):143–54. https://doi.org/10.1016/j.cden.2017.09.001.

29. Chen H, Cantor A, Meyer J, Beth Corcoran M, Grendys E, Cavanaugh D, et al. Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer. 2003;97(4):1107–14. https://doi.org/10.1002/cncr.11110.

30. Extermann M, Chen H, Cantor AB, Corcoran MB, Meyer J, Grendys E, et al. Predictors of tolerance to chemotherapy in older cancer patients: a prospective pilot study. Eur J Cancer. 2002;38(11):1466–73. https://doi.org/10.1016/S0959-8049(02)00000-4.

31. Buja A, Lago L, Lago S, et al. Marital status and stage of cancer at diagnosis: A systematic review. Eur J Cancer Care (Engl). 2018;27:e12755. https://doi.org/10.1111/ecc.12755.

32. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex, and age-based disparities. JAMA. 2004;291(22):2720–6. https://doi.org/10.1001/jama.291.22.2720.

33. Kivdal O. The poorer cancer survival among the unmarried in Norway: is much explained by comorbidities? Soc Sci Med. 2013;81:42–52. https://doi.org/10.1016/j.socscimed.2013.01.012.

34. Goodwin JS, Hunt WC, Key CR, Samet JM. The effect of marital status on stage, treatment, and survival of cancer patients. JAMA. 1987;258(21):3125–30. https://doi.org/10.1001/jama.1987.03400210067027.

35. Aizer AA, Chen MH, McCarthy EP, et al. Marital status and survival in patients with cancer. J Clin Oncol. 2013;31(31):4981–5. https://doi.org/10.1200/JCO.2013.51.4988.

36. Neuman MD, Werner RM. Marital status and postoperative functional recovery. JAMA Surg. 2016;151(2):194–6. https://doi.org/10.1001/jamasurg.2015.3420.

37. Eskander ME, Schapira EF, Bliss LA, Burish NM, Tadikonda A, Ng SC, et al. Keeping it in the family: the impact of marital status and next of kin on cancer treatment and survival. Am J Surg. 2016;212(4):691–9. https://doi.org/10.1016/j.amjsurg.2016.07.004.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.