

Jan 23, 2019

Prof. Dennis A Bloomfield and Prof. Sandro Vento,  
Editors-in-Chief  
*World Journal of Clinical Cases*

Dear Dr. Dennis A Bloomfield and Dr. Sandro Vento,

**Subject: Submission of revised manuscript (reference No. 42867), “Induction chemotherapy with docetaxel, cisplatin and fluorouracil (TPF) followed by concurrent chemoradiotherapy for unresectable sinonasal undifferentiated carcinoma: report of two cases and review of the literature”.**

We wish to express our appreciation to the Reviewers for their insightful comments, which have enabled us to improve our paper greatly. Below are our point-by-point responses to each of the comments and questions of the Reviewers. Changes in the manuscript are shown highlighted in red.

We hope the revised version would be suitable for publication and look forward to hearing from you.

Sincerely,

**Sho Watanabe, MD**

Department of Head and Neck Medical Oncology, National Cancer Center  
Hospital, 1-1, Tsukiji 5, Chuo-ku, Tokyo, Japan

Telephone: 81-3-3542-2511

E-mail: sh.watanabe02@gmail.com

Phone: +81-3-3542-2511

## **Reviewer 1 (03656272)**

### **Comment:**

*In the title, abbreviation shouldn't be used. "docetaxel, cisplatin and fluorouracil (TPF)" should be used.*

### **Response:**

We have replaced "TPF" with "docetaxel, cisplatin and fluorouracil (TPF)" in the title.

### **Comment:**

*Reference 1 should be carefully revised.*

### **Response:**

The possibility of cases being at the T4 stage and having cervical lymph node metastasis differed among studies. Thus, we have added the following references into the sentence to correctly describe the tendency of tumor spread.

2. Gray ST, Herr MW, Sethi RK, Diercks G, Lee L, Curry W, Chan A, Clark J, Holbrook EH, Rocco J, Sadow PM, Lin DT: Treatment outcomes and prognostic factors, including human papillomavirus, for sinonasal undifferentiated carcinoma: a retrospective review. *Head Neck* 2015; 37: 366-74 [PMID: 24421248 DOI: 10.1002/hed.23606]

3. Lopez F, Suarez V, Vivanco B, Suarez C, Llorente JL: Current management of sinonasal undifferentiated carcinoma. *Rhinology* 2015; 53: 212-20. [PMID: 26363162 DOI: 10.4193/Rhin14.054]

### **Comment:**

*In the case 1/2; the possible comorbidities or any risk factor for malignancy should be discussed.*

### **Response:**

We have added the following sentences in the case presentation.

*History of past illness*

Both patients had no remarkable history of illness. They were current smokers.

### **Comment:**

*Please add a reference for the TNM staging.*

**Response:**

We have added the following reference for the staging.

6. International Union Against Cancer. UICC TNM classification of malignant tumours. 7th ed. Sobin LH, Gospodarowicz MK, and Wittekind C, editor. Wiley-Blackwell: A John Wiley & Sons, Ltd., Pub (UK), 2009: 46-50.

**Reviewer 2 (02445450)**

**Comment #1-1:**

*Please provide how the authors collected references used in Table 1. What years, terms, and websites were used?*

**Response:**

We have clarified how we performed the literature review by adding the following sentences.

...In order to investigate the efficacy of induction chemotherapy plus chemoradiotherapy, we undertook a review of the literature using PubMed (Table 1). The search terms used were “sinonasal undifferentiated carcinoma” and “SNUC”. All SNUC cases published until November 2018 were included in the search. Then, the data of patients receiving induction chemotherapy plus chemoradiotherapy were extracted. Cases in which treatment options or outcomes were not individually described were excluded from the review.

**Comment #1-2:**

*Please contain consensus on induction chemotherapy prior to CRT for SNUC or nasopharyngeal carcinoma, stated in publications and guidelines.*

**Response:**

We have described the current consensus on management of SNUC and nasopharyngeal carcinoma more clearly using the following sentences and references.

... In unresectable LA-SNUC cases, definitive chemoradiotherapy alone has been widely used<sup>[3]</sup>, but it has shown less promising efficacy than the multimodality treatment that includes surgery<sup>[5]</sup>.

...A small number of LA-SNUC patients received induction chemotherapy prior to chemoradiotherapy which is recommended for locally advanced nasopharyngeal carcinoma patients<sup>[19]</sup>.

3. Lopez F, Suarez V, Vivanco B, Suarez C, Llorente JL: Current management of sinonasal undifferentiated carcinoma. *Rhinology* 2015; 53: 212-20. [PMID: 26363162 DOI: 10.4193/Rhin14.054]

5. Christopherson K, Werning JW, Malyapa RS, Morris CG, Mendenhall WM: Radiotherapy for sinonasal undifferentiated carcinoma. *Am J Otolaryngol* 2014; 35: 141-6 [PMID: 24268566 DOI: 10.1016/j.amjoto.2013.10.001]

19. Colevas AD, Yom SS, Pfister DG, Spencer S, Adelstein D, Adkins D, Brizel DM, Burtness B, Busse PM, Caudell JJ, Cmelak AJ, Eisele DW, Fenton M, Foote RL, Gilbert J, Gillison ML, Haddad RI, Hicks WL, Hitchcock YJ, Jimeno A, Leizman D, Maghami E, Mell LK, Mittal BB, Pinto HA, Ridge JA, Rocco J, Rodriguez CP, Shah JP, Weber RS, Witek M, Worden F, Zhen W, Burns JL, Darlow SD: NCCN guidelines insights: head and neck cancers, version 1. 2018. *J Natl Compr Canc Netw* 2018; 16: 479-90. [PMID: 29752322 DOI: 10.6004/jnccn.2018.0026]

#### **Comment #2:**

Please include more recent references and state comments on this, e.g. *J Clin Oncol* 2019 Jan 7 (JCO 1800353).

#### **Response:**

We have included the following references published since 2013.

10. de Bonnecaze G, Verillaud B, Chaltiel L, Fierens S, Chapelier M, Rumeau C, Melard O, Gavid M, Dufour X, Righini C, Uro-coste E, Rives M, Bach C, Baujat B, Janot F, de Gabory L, Vergez S: Clinical characteristics and prognostic factors of sinonasal undifferentiated carcinoma: a multicenter study. *Int Forum Allergy Rhinol* 2018; 8: 1065-72 [PMID: 29935059 DOI: 10.1002/alr.22143]

20. Gamez ME, Lal D, Halyard MY, Wong WW, Vargas C, Ma Daniel, Ko SJ, Foote RL, Patel SH: Outcomes and patterns of failure for sinonasal

undifferentiated carcinoma (SNUC): The Mayo Clinic Experience. *Head Neck* 2017; 39: 1819-24. [PMID: 28561906 DOI: 10.1002/hed.24834]

21. Amit M, Abdelmeguid AS, Watcherporn T, Takahashi H, Tam S, Bell D, Ferrarotto R, Glisson B, Kupferman ME, Roberts DB, Su SY, Raza SM, DeMonte F, Hanna EY: Induction chemotherapy response as a guide for treatment optimization in sinonasal undifferentiated carcinoma. *J Clin Oncol* 2019; Jan 7: JCO1800353. [PMID: 30615549 DOI: 10.1200/JCO.18.00353]

23. Ansari M, Guo S, Fakhri S, Citardi MJ, Blanco A, Patino M, Buryanek J, Amato R, Karni R, Brown RE: Sinonasal undifferentiated carcinoma (SNUC): morphoproteomic-guided treatment paradigm with clinical efficacy. *Ann Clin Lab Sci* 2013; 43: 45-53. [PMID: 23462605]

24. Sienna J, Nguyen NT, Arsenault J, Hodson I, Meyers B: A Case of sinonasal undifferentiated carcinoma with brain metastases. *Cureus* 2018; 10: e2320. [PMCID: PMC5947934 DOI: 10.7759/cureus.2320]

Also, we mentioned the novel treatment approach reported in JCO 2019 in the following sentence.

...A recently published study also demonstrated the intriguing finding that in patients who responded to induction chemotherapy, definitive chemoradiotherapy provided a better chance of disease control and improved survival than did surgical resection<sup>[21]</sup>, suggesting the possibility that definitive chemoradiotherapy can replace surgery even in resectable LA-SNUC cases.

**Comment #3:**

Please state comments on Guidelines, such as NCCN Guidelines Insights: Head and Neck Cancers, Version 1. 2018.

**Response:**

We have added the following sentence including the guideline reference.

...A small number of LA-SNUC patients received induction chemotherapy prior to chemoradiotherapy, which is recommended for locally advanced nasopharyngeal carcinoma patients<sup>[19]</sup>.

### **Reviewer 3 (00182114)**

#### **Comment #1:**

*Two cases were not affected cervical lymphonode. Please tell me the reason why two cases are recurrence free for 44 months.*

#### **Response:**

A recently published study showed that IMRT was associated with longer survival of LA-SNUC patients. Thus, we suggest that the use of IMRT contributed to the improved outcome in our cases. We mentioned this possibility in the following sentences.

... Compared with the previous cases, our cases showed improved survival. In addition to the effect of the TPF induction chemotherapy, IMRT may contribute to the outcome.

... Retrospective studies indicated the crucial role of IMRT, showing that the use of IMRT was related to longer survival of SNUC patients<sup>[10, 20]</sup>.

Currently, the prognostic role of N stage for SNUC remains unknown. We have added the following sentence.

...but the prognostic feature of cervical lymph node metastasis also remains controversial<sup>[10]</sup>.

#### **Comment #2:**

*Author's data is promising strategy for advanced stage SNUC. I think TPF followed by CCRT should be performed for resectable SNUC instead of surgical resection. How about this opinion?*

#### **Response:**

A retrospective study published in JCO 2019 showed that in patients who responded to induction chemotherapy, definitive CCRT provided better outcome than did surgical resection, suggesting the possibility that CCRT can replace surgery in this setting. We added the following sentences to address the issue.

... A recently published study also demonstrated the intriguing finding that in patients who responded to induction chemotherapy, definitive chemoradiotherapy provided a better chance of disease control and improved survival than did surgical resection<sup>[21]</sup>, suggesting the possibility that definitive chemoradiotherapy can replace surgery even in resectable LA-SNUC cases.

...This treatment option should be a curative alternative to surgery for LA-SNUC patients.

**Comment #3:**

*Please tell me which is more important factor of the prognosis of SNUC , T or N.?*

**Response:**

Finding the difference in prognostic significance between the T and N staging is challenging because the prognostic role of T/N staging for SNUC remains unclear. A European multicenter study published in 2018 showed that clinical staging according to UICC T or N classification was not associated with patient survival. Instead of staging, the use of induction chemotherapy significantly contributed to the improved outcome. The chemo-sensitive nature of SNUC may challenge the utility of T and N staging. Furthermore, a conflicting result was reported regarding the N classification. A meta-analysis revealed that the neck involvement was related to lower survival rates in Kadish C patients. Taken together, current evidence does not show sufficient data to associate T/N staging with patient survival. We have added the following sentences to describe this aspect.

... The prognostic factors for LA-SNUC remain unclear. UICC TNM staging of head and neck cancer has long been applied to SNUC, but the T staging on admission was not prognostic<sup>[10]</sup>. Our cases with T4 disease showed improved survival, possibly because they were down-staged by induction TPF chemotherapy and received subsequent chemoradiotherapy. The impact of local tumor spread on survival should be further investigated.

...but the prognosis for cervical lymph node metastasis still remains controversial. Two retrospective studies reported conflicting results: the neck involvement was associated with lower survival in Kadish C patients in a

meta-analysis<sup>[4]</sup>. In contrast, no significant difference in survival was shown between N0 and N1-2 patients in a multicenter study<sup>[10]</sup>.

#### **Reviewer 4 (00058381)**

##### **Comment:**

*The results of the literature review which is provided in the discussion also underline that more research on this topic is needed.*

##### **Response:**

The choice of induction regimens differed among institutions and is left to the discretion of the treating physicians. Therefore, we have added the following sentence.

... As the chemotherapeutic regimens differ among institutions and the choice of regimen is often made by the treating physicians, more research is needed in order to establish the optimal induction regimen.

##### **Comment:**

*The title ("A case report and review of the literature") should be changed to "Two case reports..." or "Report of two cases..."*

##### **Response:**

We replaced "a case report" with "report of two cases" in the title.

##### **Comment:**

*"...an 80%-reduced dose (80 mg/m<sup>2</sup>) due to the prolonged anorexia caused by the prior TPF chemotherapy." – "80%-reduced" sounds like "reduced by 80%"; therefore writing "a dose reduced to 80%" is suggested.*

##### **Response:**

We replaced "80%-reduced" with "a dose reduced to 80%".

##### **Comment:**

*Table 1: "3-dimentional conformal radiotherapy" -> "3-dimensional conformal radiotherapy".*

##### **Response:**

We replaced "3-dimentional conformal radiotherapy" with "3-dimensional conformal radiotherapy".