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SPECIAL ARTICLE

Pan-Asian adaptation of the EHNS–ESMO–ESTRO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with squamous cell carcinoma of the head and neck

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The most recent version of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of squamous cell carcinoma (SCC) of the oral cavity, larynx, oropharynx and hypopharynx was published in 2020. It was therefore decided by both the ESMO and the Korean Society of Medical Oncology (KSMO) to convene a special, virtual guidelines meeting in July 2021 to adapt the ESMO 2020 guidelines to consider the potential ethnic differences associated with the treatment of SCCs of the head and neck (SCCHN) in Asian patients. These guidelines represent the consensus opinions reached by experts in the treatment of patients with SCCHN (excluding nasopharyngeal carcinomas) representing the oncological societies of Korea (KSMO), China (CSCO), India (ISMPO), Japan (JSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). The voting was based on scientific evidence and was independent of the current treatment practices and drug access restrictions in the different Asian countries. The latter was discussed when appropriate. This manuscript provides a series of expert recommendations (Clinical Practice Guidelines) which can be used to provide guidance to health care providers and clinicians for the optimisation of the diagnosis, treatment and management of patients with SCC of the oral cavity, larynx, oropharynx and hypopharynx across Asia.

Key words: ESMO, guidelines, head and neck, Pan-Asian, squamous cell carcinoma, treatment

INTRODUCTION

In 2020 an estimated 19.3 million new cases of cancer were diagnosed and almost 10 million cancer-related deaths recorded, worldwide.[1] Of these, squamous cell carcinomas of the head and neck (SCCHN) including carcinomas of the lip, oral cavity, larynx, oropharynx and hypopharynx, but excluding nasopharyngeal cancer, accounted for 3.9% (744 994) of new cases across both sexes, and 3.7%

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(357.339) of cancer deaths.[1] The highest incidence of head and neck cancer (HNC) is seen in Asia, with deaths from HNCs accounting for >5% of all cancer deaths. HNC comprises a heterogenous group of malignancies and the prevalences of the different types of HNCs vary from country to country across Asia. For example China and Taiwan have high incidences of oral cavity cancers, with the latter having increasing rates of human papilloma virus (HPV)-related oropharyngeal cancer.[2,3] India currently contributes ~60% of the HNC cases worldwide with HNC the most common cancer in Indian men, and cancer of the oral cavity the most prevalent. In South Korea, laryngeal cancer is the commonest form of HNC with the incidence of all HNCs (tonsil, hypopharynx, oropharynx and larynx cancer) increasing, with a higher incidence in men than in women.[4] In Japan alone, there are >39 000 cases of HNC and ~10 000 deaths from the disease, annually.[5,6] A report from the Japan Society for Head and Neck Cancer Registry Committee on 11 716 previously untreated HNC patients registered in 2016 showed ~83% of the cases to be accounted for by tumours of the oral cavity (24.9%), larynx (20.4%), hypopharynx (21.4%) and oropharynx (16.9%).[7]

Although the incidence varies between countries and individual regions within countries, ~80% of cases of SCCHN worldwide are attributable to tobacco use, excessive alcohol consumption or both, and in South Asia the use of smokeless tobacco and betel quid/areca nut products.[8] Betel quid/areca nut use has been linked to high rates of cancers of the oral cavity in India, Taiwan and some provinces of mainland China.[9] Other risk factors include environmental pollutants, especially in countries with worsening air pollution such as India[10] and China,[11] and HPV infections in the aetiology of oropharyngeal cancer and cancers of the oral cavity.[12] A recent meta-analysis looking at the prevalence of HPV-related oropharyngeal cancers in the Asia Pacific region reported an overall prevalence of 40.53% for oropharyngeal cancers.[13] In a Malaysian study of 60 patients with oropharyngeal cancer of whom 53.3% were of Chinese ethnicity, 35% of Indian ethnicity and 11.7% of Malay ethnicity, all the Indian patients had p16-negative disease.[14] This was consistent with a study of 88 patients with SCCHN conducted in South India in which only 2.6% cases were HPV/p16-positive.[15] Significantly, in the Malaysian study[14] 80% of the HPV-positive cases were in Chinese patients and the prevalence of p16-positive oropharyngeal squamous cell carcinomas (SCC) across all three ethnicities was half that of a matched UK cohort (25% versus 49%).[14] A study conducted in Singapore involving 159 urban, multiethnic, South East Asian patients with SCCHN demonstrated a high prevalence of high-risk HPV variants (HPV16, 18, 31, 45, 56 and 68) and confirmed that HPV16 and p16 immunohistochemical expression were predominantly detected in the oropharyngeal carcinomas.[16] Although an ethnic predisposition cannot be excluded, the differences in HPV positivity between the different Asian populations is probably due to differences in sexual practices.

Guidelines and recommendations for the treatment and management of patients with SCCHN in Asia have been published for India,[17,18] China,[19] Japan,[20] Malaysia[21] and Taiwan[22] and are important for the standardisation of both diagnostic and treatment approaches, with the aim of optimising clinical outcomes for what is an increasing health care problem in Asia. The European Society for Medical Oncology (ESMO) guidelines for the diagnosis treatment and follow-up of patients with SCCs of the oral cavity, larynx, oropharynx and hypopharynx (excluding nasopharyngeal carcinomas), prepared in conjunction with the European Head and Neck Society (EHNS) and the European Society for Radiotherapy and Oncology (ESTRO), were published in October 2020,[23] and a decision was taken by ESMO and the Korean Society of Medical Oncology (KSMO) that these guidelines should be adapted for patients of Asian ethnicity. Consequently, representatives of KSMO, ESMO, ESTRO, the Chinese Society of Clinical Oncology (CSCO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Japanese Society of Medical Oncology (JSMO), the Malaysian Oncological Society (MOS), the Singapore Society of Oncology (SSO) and the Taiwan Oncology Society (TOS) convened for a virtual working meeting ('face-to-face' meeting) on 24 July 2021, hosted by KSMO, to adapt the recent EHNS-ESMO-ESTRO Clinical Practice Guidelines.[23] This manuscript summarises the Pan-Asian adapted guidelines developed at the meeting accompanied by the level of evidence (LoE), grade of recommendation (GoR) and percentage consensus reached for each recommendation.

METHODOLOGY

This Pan-Asian adaptation of the current ESMO Clinical Practice Guidelines[23] was prepared in accordance with the principles of ESMO standard operating procedures (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology) and was a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS.

Representatives from KSMO ($n = 4$), ESMO ($n = 7$), EHNS ($n = 1$), ESTRO ($n = 2$) and two experts from each of the oncological societies of China (CSCO), India (ISMPO), Japan (JSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS) convened for the virtual 'face-to-face' meeting. Only two of the members from KSMO (HRK and YGL) were allowed to vote on the recommendations together with the experts from each of the six other Asian oncology societies ($n = 14$).

A modified Delphi process was used to review, accept or adapt each of the individual recommendations in the latest EHNS-ESMO-ESTRO Clinical Practice Guidelines.[23] The 14 Asian experts were asked to vote YES or NO (one vote per society) on the 'acceptability' (agreement with the scientific content of the recommendation) and 'applicability' (availability, reimbursement and practical challenges) of each of the ESMO recommendations in a pre-meeting survey (see Supplementary Methodology, available at https://doi.org/10.1016/j.esmoop.2021.100309). For recommendations, where a consensus was not reached, the Asian experts were invited to modify the wording of the recommendation(s) at the virtual 'face-to-face' meeting using rounds of voting in

order to determine the definitive acceptance or rejection of an adapted recommendation and discuss the applicability challenges. The 'Infectious Diseases Society of America-United States Public Health Service Grading System' (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100309)[24] was used to define the LoE and strength (grade) of each recommendation. Any modifications to the initial recommendations were highlighted in bold text in a summary table of the final Asian recommendations and in the main text, if and as applicable. A consensus was considered to have been achieved when ≥80% of experts voted that a recommendation was acceptable.

RESULTS

In the initial pre-meeting survey, the 14 Asian experts reported on the 'acceptability' and 'applicability' of the 32 recommendations for the diagnosis treatment and follow-up of patients with SCCHN of the oral cavity, larynx, oropharynx and hypopharynx from the 2020 EHNS-ESMO-ESTRO Clinical Practice Guidelines.[23] These recommendations were made in the four categories listed below:

- Diagnosis and pathology/molecular biology (Recommendations 1a-f)
- Staging and risk assessment (Recommendation 2)
- Treatment (Recommendations 3a-v)
- Follow-up (Recommendations 4a-c)

A lack of agreement in the pre-meeting survey was initially established for 'recommendations 3i and 3v' (with no consensus for 'acceptability') (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100309) and 'recommendations 1c, 1d, 1f, 3b, 3i, 3m, 3n, 3s, 3t, 3u, 3v and 4c' (with no consensus for 'applicability') (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100309). After further consideration, however, the 'recommendations 3i and 3v', and 'recommendations 1d, 3a, 3e, 3f, 3k, 3l 3m, 3n, 3r, 3s, 3t and 4c' were identified for discussion during the 'face-to-face' meeting, based on the comments and feedback from the initial pre-meeting survey, as it was clear that some of the comments made in terms of applicability had scientific relevance. It was also decided that there was no need to discuss 'recommendations 1c, 1f, 3b and 3u' initially identified for discussion in terms of applicability.

1. Diagnosis and pathology/molecular biology—Recommendations 1a-f

The Pan-Asian panel of experts agreed with and 'accepted' completely (**100% consensus**) the EHNS-ESMO-ESTRO recommendations on screening, 'recommendations 1a-f' from a scientific point of view (see below and Table 1).

1a. Clinical examination and pathological confirmation are mandatory [IV, A].

1b. Rigid head and neck endoscopy, head and neck contrast-enhanced computed tomography (CE-CT) and/or magnetic resonance imaging (MRI) and chest imaging (with CT and/or [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) are strongly recommended [IV, A].

1c. For oropharyngeal cancer, p16 immunohistochemistry (IHC) is strongly recommended [I, A].

1d. For SCCHN of unknown primary, p16 and Epstein—Barr-encoded RNA (EBER) are recommended. If p16 staining is positive, another specific HPV test **may** be carried out to confirm the HPV status [III, **B**].

1e. On the surgical specimens, depth of invasion of oral cavity cancer, assessment of the number of invaded lymph nodes as well as the presence extracapsular extension, perineural and lymphatic infiltration and the surgical margins must be evaluated [I, A].

1f. For recurrent and/or metastatic SCCHN, tumour programmed death-ligand 1 (PD-L1) expression should be evaluated [II, B].

The experts from the oncological societies of Japan, Singapore and China, however, did not agree that an HPV test had to be carried out (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100309), and in the wording of 'recommendation 1d' above 'should' was replaced by '**may**' as per bold text above and Table 1, and the GoR changed from A to B.

2. Staging and risk assessment—Recommendation 2

The Pan-Asian panel of experts agreed with and 'accepted' completely (**100% consensus**) the EHNS-ESMO-ESTRO recommendations on staging and risk assessment, 'recommendation 2a' (below and Table 1) from both a scientific (acceptability) and applicability point of view (see also Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100309).

2a. The UICC TNM 8th edition staging system should be used (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100309).[25]

3. Treatment—Recommendations 3a-v

The Pan-Asian panel of experts agreed with and 'accepted' completely (**100% consensus**) the EHNS-ESMO-ESTRO recommendations on treatment, 'recommendations 3b-d, g, h, j, o-q and u,' from a scientific point of view (see below and Table 1). A lack of consensus in terms of 'acceptability' for recommendations 3i and 3v was identified, however, from the time of the pre-meeting survey and the need for discussion for 'recommendations 3a, e, f, k, l, m, n, r, s and t' from a scientific perspective only after consideration of the feedback comments (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2021.100309), as described above.

With regard to 'recommendation 3a' there was concern that not all centres in Asia have multidisciplinary teams (MDT) for the treatment of HNC, so the wording of the recommendation was revised slightly as per the bold text below with 100% consensus. After discussion at the

Table 1. Summary of Asian recommendations

Recommendations	Acceptability consensus (%)
Recommendation 1: Diagnosis and pathology/molecular biology	
1a. Clinical examination and pathological confirmation are mandatory [IV, A].	100
1b. Rigid head and neck endoscopy, head and neck CE-CT and/or MRI and chest imaging (with CT and/or FDG-PET) are strongly recommended [IV, A].	100
1c. For oropharyngeal cancer, p16 IHC is strongly recommended [I, A].	100
1d. For SCCHN of unknown primary, p16 and EBER are recommended. If p16 staining is positive, another specific HPV test **may** be carried out to confirm the HPV status [III, **B**].	100
1e. On the surgical specimens, DOI of oral cavity cancer, assessment of the number of invaded lymph nodes as well as the presence extracapsular extension, perineural and lymphatic infiltration and the surgical margins must be evaluated [I, A].	100
1f. For recurrent and/or metastatic SCCHN, tumour PD-L1 expression should be evaluated [II, B].	100
Recommendation 2: Staging and risk assessment	
2. The UICC TNM 8 staging system should be used.	100
Recommendation 3: Treatment	
3a. **Ideally** the optimal treatment strategy **should** be discussed in an MDT including not only the treating physicians but all the supportive specialities [III, A].	100
3b. Patients should be treated at high-volume facilities [II, A].	100
3c. In the case of RT, all patients should be treated by IMRT or VMAT [I, A].	100
3d. The treatment strategy for HPV-positive SCCHN should be the same as for HPV-negative SCCHN [I, A].	100
3e. The recommended treatment option should be based on patient- and treatment-related factors (e.g. side-effects, complications, etc.) since conservative surgery and RT may often provide similar locoregional control [IV, A].	100
3f. Early disease should be treated as much as possible with a single-modality treatment [IV, A].	100
3g. Standard options for locally advanced disease are either surgery plus adjuvant (C)RT or primary concomitant CRT [I, A].	100
3h. Primary surgical treatment followed by RT or CRT is the preferred treatment for T3/T4 oral cavity and T4 laryngeal cancers [III, A].	100
3i. A hypoxic radiosensitiser, **if available, might be considered to** increase locoregional control and disease-free survival compared with RT alone [I, **C**].	100
3j. Concomitant CRT increases locoregional control and overall survival compared with RT alone [I, A].	
3k. The standard of care for chemotherapy is cisplatin at a dose of 100 mg/m^2 given on days 1, 22 and 43 of concomitant RT [II, A]. **Weekly cisplatin 40 mg/m^2 is an alternative option in the post-operative setting [II, A].**	100
3l. In patients unfit for cisplatin, carboplatin combined with 5-FU or cetuximab concomitant to RT as well as hyperfractionated or accelerated RT without chemotherapy are treatment alternatives [II, A].	100
3m. For larynx preservation, induction chemotherapy with TPF (**up to** three courses **according to response**) followed by RT alone is a validated treatment option [I, A].	100
3n. Besides larynx preservation, induction chemotherapy is not routinely recommended.	100
3o. Neck dissection is not recommended in cases of negative FDG-PET and normal size lymph nodes at 12 weeks after CRT [I, A].	100
3p. Post-operative RT is recommended for patients with pT3-4 tumours, resection margins with macroscopic (R2) or microscopic (R1) residual disease, perineural infiltration, lymphatic infiltration, >1 invaded lymph node and the presence of extracapsular infiltration [II, A].	100
3q. Post-operative CRT is recommended for patients with an R1 resection and extranodal extension [I, A].	100
3r. **Every effort should be made to ensure that the administration of** post-operative RT or CRT starts within 6 weeks of surgery [II, A].	100
3s. Pembrolizumab in combination with platinum/5-FU and pembrolizumab monotherapy are two approved regimens for patients with R/M SCCHN expressing PD-L1 (CPS ≥1) [I, A; ESMO-MCBS v1.1 score: 4]. **The choice of pembrolizumab monotherapy or chemotherapy plus pembrolizumab may be based on CPS, tumour burden and symptoms [V, C**].	100
3t. Platinum/5-FU/cetuximab remains the standard therapy for patients with R/M SCCHN not expressing PD-L1 [I, A; ESMO-MCBS v1.1 score: 3]. **Pembrolizumab plus chemotherapy [II, C], TPeX [II, B] and PCE [II, B] are also treatment options in this population.**	100
3u. Nivolumab is both FDA- and EMA-approved for recurrent/metastatic patients who progress within 6 months of platinum therapy [I, A; ESMO-MCBS v1.1 score: 4].	100
3v. **According to the specific genetic profile of the Asian patient population, DPD genotyping or phenotyping may be considered before initiating fluoropyrimidine-based therapy [III, C].**	100
Recommendation 4: Follow-up	
4a. Clinical follow-up including head and neck examination by flexible endoscopy should be carried out every 2-3 months during the first 2 years, every 6 months for years 3-5 and annually thereafter [III, A].	100
4b. Imaging should be carried out if symptoms occur or in cases of abnormalities found at the clinical examination [III, A].	100
4c. FDG-PET/CT is recommended 3 months after CRT for patients with node-positive disease to assess the necessity of neck dissection [I, A].	100

CE-CT, contrast-enhanced-computed tomography; CPS, combined positive score; CRT, chemoradiotherapy; CT, computed tomography; DOI, depth of invasion; DPD, dihydropyrimidine dehydrogenase; EMA, European Medicines Agency; EBER, Epstein—Barr-encoded RNA; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; FDG-PET, 2-fluoro-2-deoxy-D-glucose-positron emission tomography; 5-FU, 5-fluorouracil; HPV, human papilloma virus; IHC, immunohistochemistry; IMRT, intensity modulated radiotherapy; MDT, multidisciplinary team; MRI, magnetic resonance imaging; PCE, paclitaxel, carboplatin and cetuximab; PD-L1, programmed death-ligand 1; R/M, recurrent/metastatic; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; TNM, tumour, node and metastasis; TPeX, taxane, cisplatin and cetuximab; TPF, docetaxel, cisplatin and 5 -FU; UICC, Union for International Cancer Control; VMAT, volumetric modulated arc therapy.

'face-to-face' meeting 'recommendations 3e and f' were accepted without change, with 100% consensus.

3a. **Ideally** the optimal treatment strategy **should** be discussed in an MDT including not only the treating physicians but all the supportive specialities [III, A; **consensus = 100%].**

3b Patients should be treated at high-volume facilities [II, A].

3c. In the case of radiotherapy (RT), all patients should be treated by intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) [I, A].

3d. The treatment strategy for HPV-positive SCCHN should be the same as for HPV-negative SCCHN [I, A].

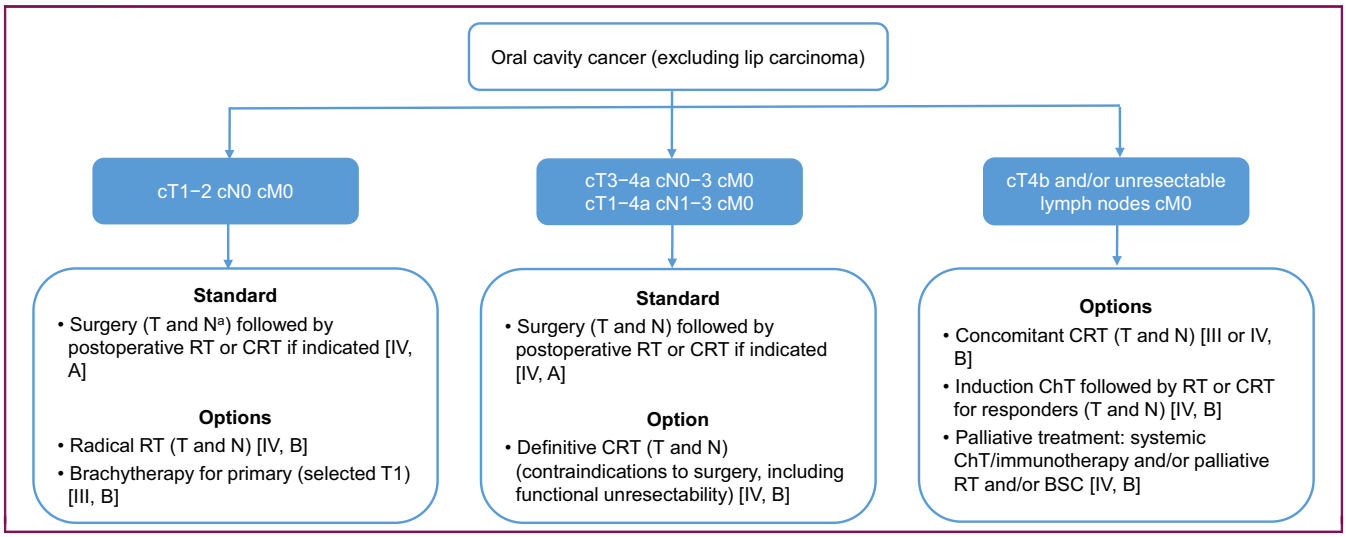

Figure 1. Management of oral cavity cancer (stage I-IVB), excluding lip carcinoma.
BSC, best supportive care; c, clinical; ChT, chemotherapy; CRT, chemoradiotherapy; DOI, depth of invasion; M, metastasis; N, node; RT, radiotherapy; T, tumour.
[a] If DOI <10 mm: sentinel lymph node biopsy is a valid option; if DOI <5 mm and cT1N0, active surveillance of the neck is a valid option.

3e. The recommended treatment option should be based on patient- and treatment-related factors (e.g. side-effects, complications, etc.) since conservative surgery and RT may often provide similar locoregional control [IV, A; **consensus = 100%**].

3f. Early disease should be treated as much as possible with a single-modality treatment [IV, A; **consensus = 100%**].

3g. Standard options for locally advanced disease are either surgery plus adjuvant chemoradiotherapy (CRT) or primary concomitant CRT [I, A].

3h. Primary surgical treatment followed by RT or CRT is the preferred treatment for T3/T4 oral cavity and T4 laryngeal cancers [III, A], Figures 1 and 2.

A lack of consensus in terms of 'acceptability' for 'recommendation 3i' below, however, was identified in the pre-meeting survey. The use of a hypoxic radiosensitiser has not been approved in China and is not practised in Singapore. The Asian experts agreed that the evidence was available to support this recommendation in the form of a meta-analysis,[26] but thought as it was conducted on older studies, that the GoR should be changed from IA to IC. The wording of the original recommendation was therefore revised from:

3i. A hypoxic radiosensitiser increases locoregional control and disease-free survival compared with RT alone [I, A].

to read as per the bold text below.

3i. A hypoxic radiosensitiser, **if available, might be considered to** increase locoregional control and disease-free survival compared with RT alone [I, **C**; **consensus = 100%**].

'Recommendation 3j' was accepted without change, with 100% consensus.

3j. Concomitant CRT increases locoregional control and overall survival compared with RT alone [I, A].

A lack of consensus was also identified in the feedback comments about 'recommendations 3k, 3l, 3m and 3n'. With regard to 'recommendation 3k, there was concern over the statement that the standard of care was 100 mg/m^2 cisplatin given on days 1, 22 and 43 of concomitant RT (70 Gy), because a weekly dose of 40 mg/m^2 cisplatin is also a standard treatment option in Asian countries. Also, weekly low dose 40 mg/m^2 cisplatin plus RT has been shown to have similar survival to 100 mg/m^2 cisplatin plus RT every 3 weeks with lower toxicity.[27] A retrospective multicentre study failed to find any difference in survival between weekly versus 3-weekly cisplatin dosing and concomitant RT,[28] although these findings are not universal,[29,30] and more prospective clinical studies are required. Also, in a separate study, weekly cisplatin plus RT versus cetuximab plus RT, showed weekly cisplatin plus concomitant RT to have superior outcomes to cetuximab plus RT.[31] A Japanese study has also shown weekly cisplatin plus RT to be non-inferior to 3-weekly cisplatin plus RT post-operatively in Japanese patients with high-risk, locally advanced SCCHN.[32] Thus, an extra line was added to 'recommendation 3k' below (see bold text below and Table 1), with 100% consensus. There was also some discussion about 'recommendation 3l' and the use of cetuximab (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2021.100309), and the observation that Asian patients are more susceptible to RT-induced mucositis. 'Recommendation 3l' was left unchanged with 100% consensus. In relation to 'recommendation 3m' the Asian experts were concerned that it should be made clear that induction chemotherapy was only to be administered for up to three cycles, according to response, with the patient's disease evaluated after every cycle. The text of 'recommendation 3m' was thus revised accordingly (see bold text), with 100% consensus. In the case of 'recommendation 3n' it was noted that although induction chemotherapy was not used routinely with larynx preservation, the Japanese experts considered induction chemotherapy an option in the

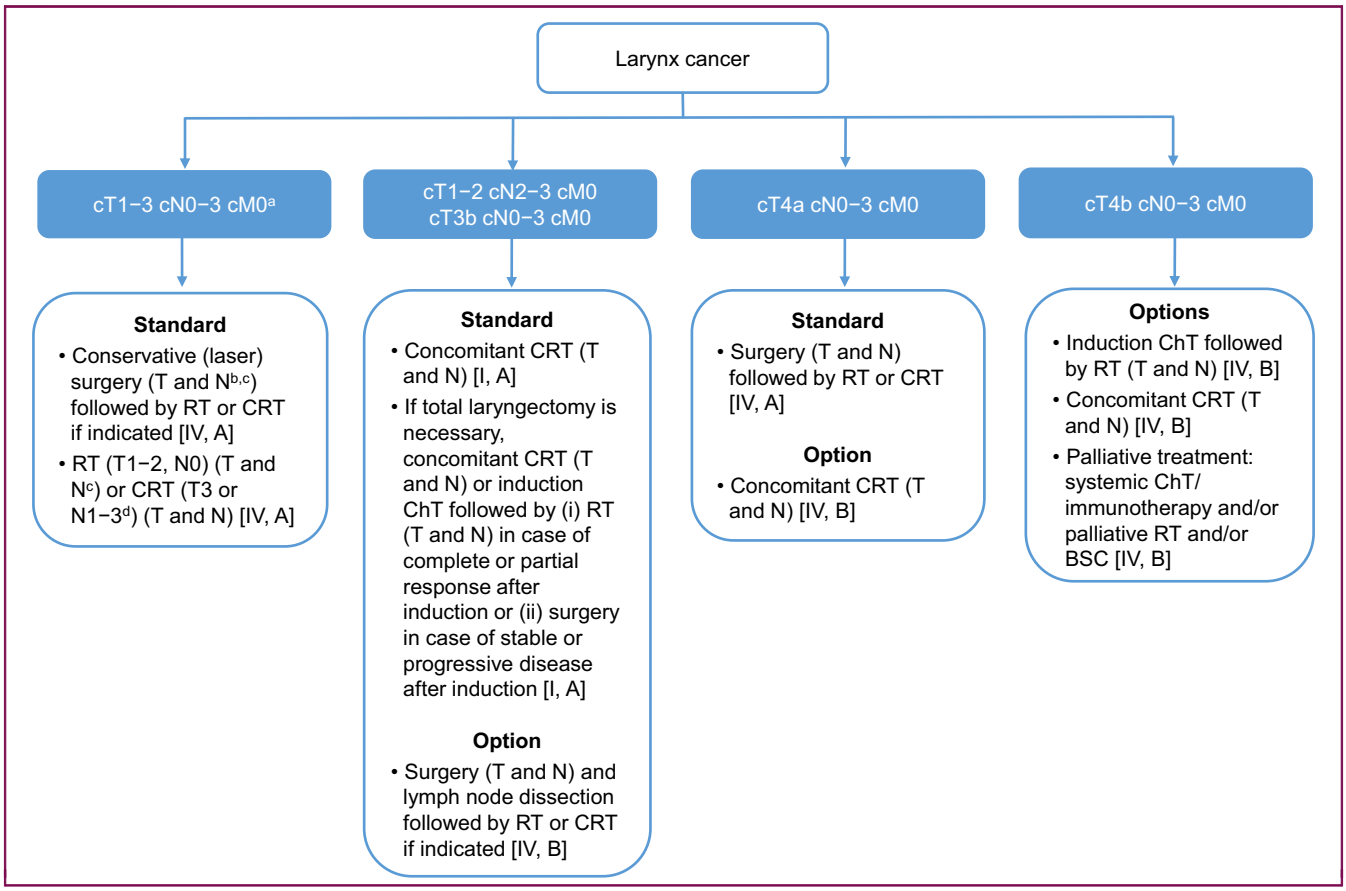

Figure 2. Management of laryngeal cancer (stage I—IVB).
BSC, best supportive care; c, clinical; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; RT, radiotherapy; T, tumour.
[a] Not requiring total laryngectomy.
[b] Requiring total laryngectomy.
[c] cT1—2N0 glottic cancer does not require neck dissection or neck RT.
[d] Altered fractionation (accelerated or hyperfractionated) RT is a valid option for selected T3 or T3N1.

case of patients with very advanced or rapidly progressive locally advanced HNC and strongly recommended induction chemotherapy for patients with a high risk of distant metastasis including N2c, N3 and level IV (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100309). The text of 'recommendation 3n' remained unchanged.

3k. The standard of care for chemotherapy is cisplatin at a dose of 100 mg/m^2 given on days 1, 22 and 43 of concomitant RT [II, A]. **Weekly cisplatin 40 mg/m^2 is an alternative option in the post-operative setting [II, A; consensus = 100%]** (Figures 3 and 4).

3l. In patients unfit for cisplatin, carboplatin combined with 5-fluorouracil (5-FU), or cetuximab concomitant to RT, as well as hyperfractionated or accelerated RT without chemotherapy, are treatment alternatives [II, A; **consensus = 100%].**

3m. For larynx preservation, induction chemotherapy with docetaxel, cisplatin and 5-FU (**up to** three courses **according to response**) followed by RT alone is a validated treatment option [I, A; **consensus = 100%].**

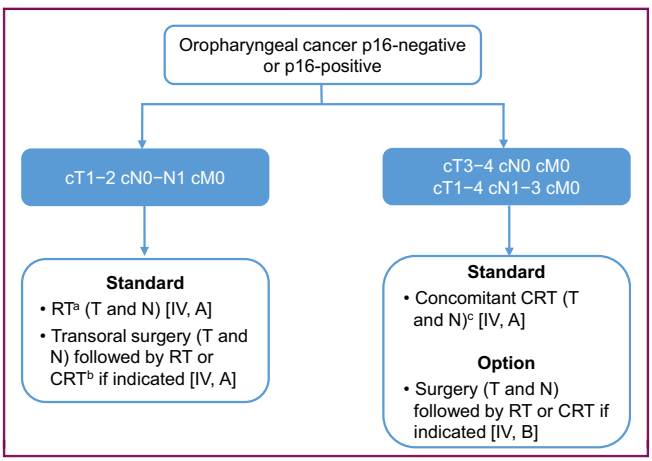

Figure 3. Management of oropharyngeal cancer (p16-negative stage I—IVB; p16-positive stage I—III).
c, clinical; CRT, chemoradiotherapy; M, metastasis; N, node; RT, radiotherapy; T, tumour.
[a] Altered fractionation (accelerated or hyperfractionated) RT is a valid option for T1—N1, T2—N0 or T2—N1.
[b] Altered fractionation (accelerated or hyperfractionated) RT is a valid option for T1—N1 or T2—N1.
[c]Altered fractionation (accelerated or hyperfractionated) RT is a valid option for T1—N1 or T2—N1.

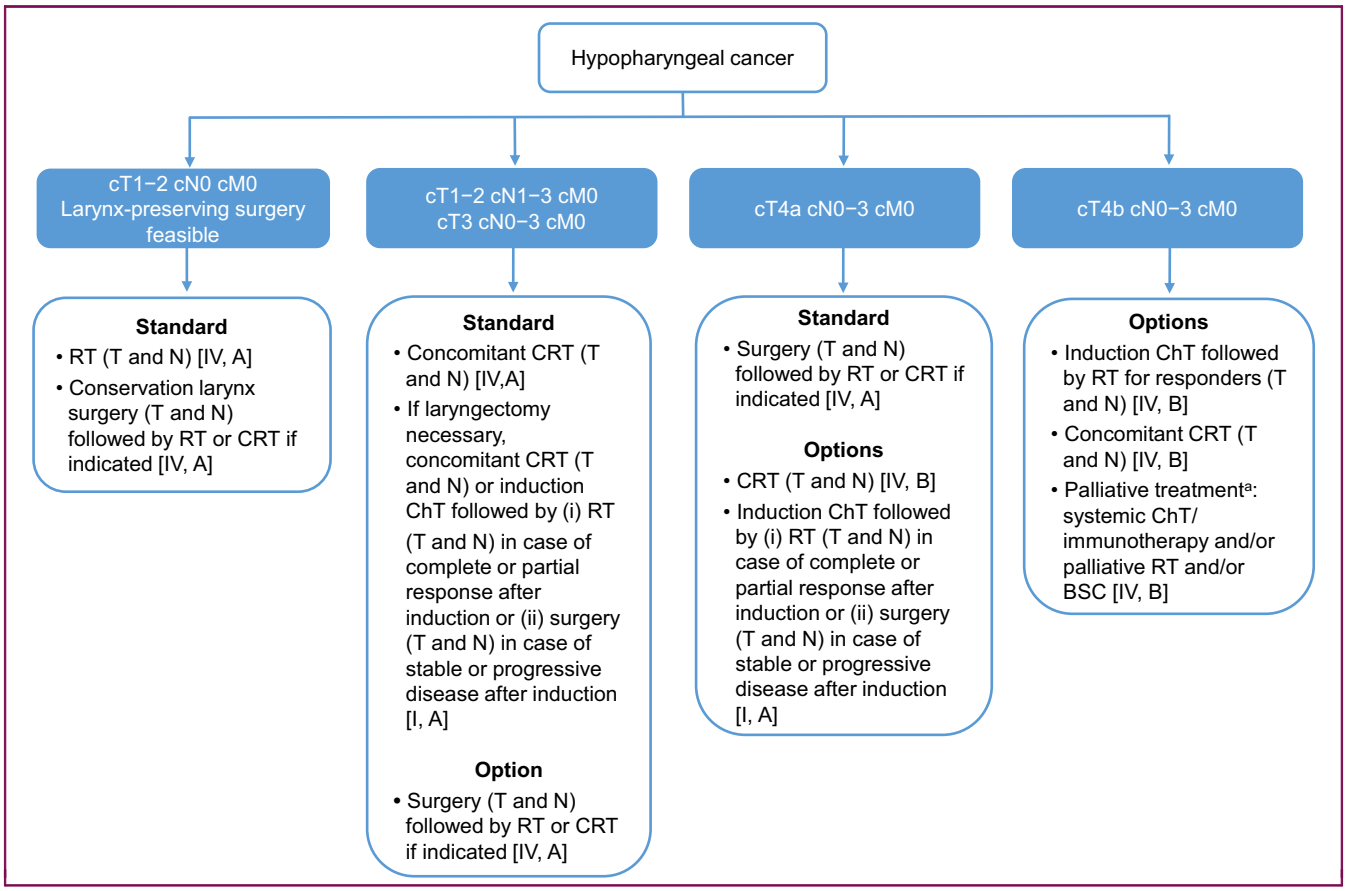

Figure 4. Management of hypopharyngeal cancer (stage I—IVB).
BSC, best supportive care; c, clinical; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; RT, radiotherapy; T, tumour.
[a]In the case of patients unfit for curative treatment. However, curative treatment should be considered for most patients.

3n. Besides larynx preservation, induction chemotherapy is not routinely recommended (Figure 2).
3o. Neck dissection is not recommended in cases of negative FDG-PET and normal size lymph nodes at 12 weeks post-CRT [I, A].
3p. Post-operative RT is recommended for patients with pT3-4 tumours, resection margins with macroscopic (R2) or microscopic (R1) residual disease, perineural infiltration, lymphatic infiltration, >1 invaded lymph node and the presence of extracapsular infiltration [II, A].
3q. Post-operative CRT is recommended for patients with an R1 resection and extranodal extension [I, A].

A lack of consensus was also identified in the feedback comments with regard to 'recommendations 3r-t, and 3v'. The Asian experts recommended that the text of 'recommendation 3r' below was revised (see bold text) to make it clear that every effort should be made to ensure that patients receive RT or CRT within 6 weeks of surgery, and definitely no later than 8 weeks after surgery. Emphasis was placed on the importance of liaising with the surgeon in an MDT environment, where and whenever possible. In relation to 'recommendation 3s' there was much discussion about the PD-L1 combined positive score (CPS) as an indicator of response to pembrolizumab based on the data from the phase III KEYNOTE (KN)-048 trial in which previously untreated patients with recurrent or metastatic SCCHN (R/M SCCHN) were randomised to receive pembrolizumab alone or chemotherapy plus either pembrolizumab or cetuximab.[33] Pembrolizumab alone improved overall survival versus chemotherapy plus cetuximab (EXTREME regimen[34]) in patients with a CPS ≥20 [median 14.9 months versus 10.7 months, hazard ratio (HR) 0.61 (95% confidence interval 0.45-0.83), $P = 0.0007$] and also in patients with a CPS ≥1 [12.3 months versus 10.3 months, HR 0.78 (0.64-0.96), $P = 0.0086$] and was non-inferior in the total population.[33] Pembrolizumab plus chemotherapy was also superior to cetuximab plus chemotherapy in terms of overall survival in the total population [13.0 months versus 10.7 months, HR 0.77 (95% confidence interval 0.63-0.93), $P = 0.0034$] with the benefit again slightly greater in patients with a CPS ≥20 than in those with a CPS ≥1 and therefore the wording of 'recommendation 3s' was revised to reflect this, and reference made to the publication by Kiyota and Imamura 2020[35] in relation to 'recommendations 3s and 3t'. Although support for the EXTREME regimen first line has been shown in a Chinese phase III study[36] and a Japanese observational study,[37] the Asian experts considered pembrolizumab plus chemotherapy to also be a valid option for the treatment of PD-L1-negative disease based on the data from the KN-048 trial,[33] for the total

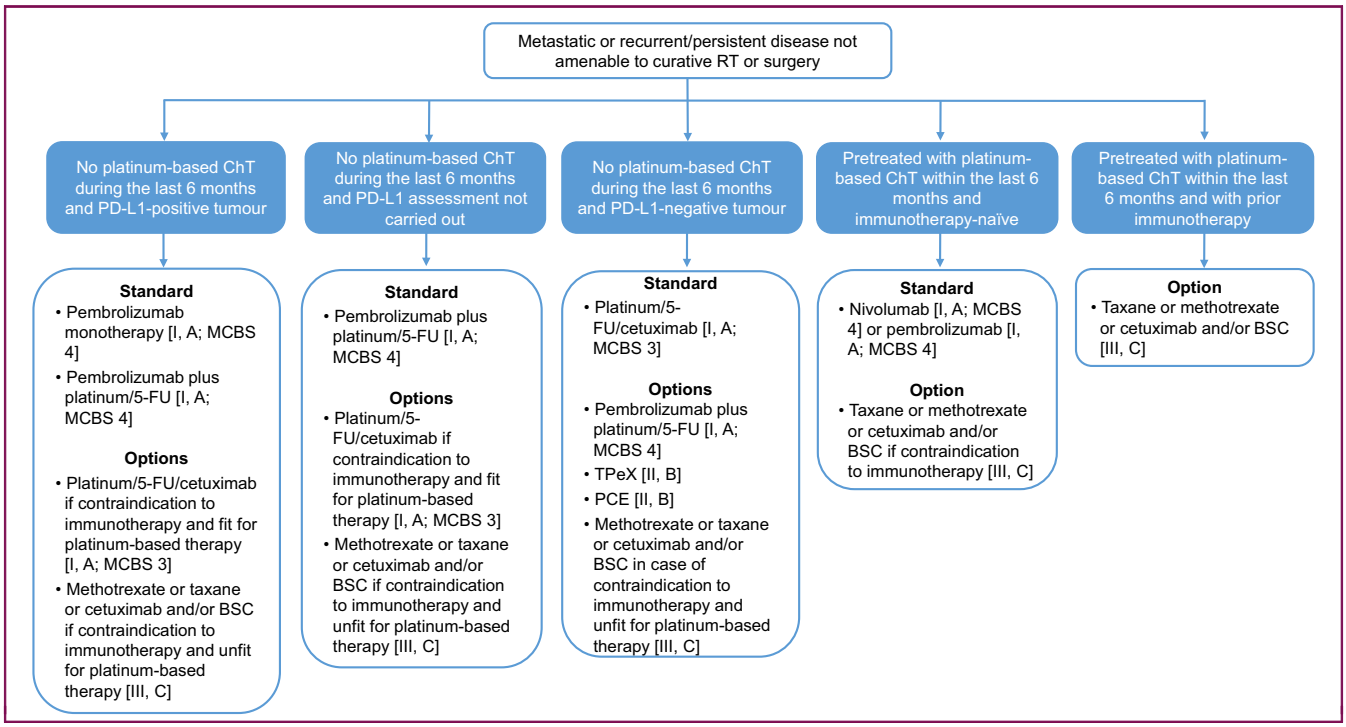

Figure 5. Management of recurrent and/or metastatic disease not amenable to curative RT or surgery.
BSC, best supportive care; c, clinical; ChT, chemotherapy; CRT, chemoradiotherapy; 5-FU, 5-fluorouracil; M, metastasis; MCBS, Magnitude of Clinical Benefit Scale; N, node; PCE, paclitaxel, carboplatin and cetuximab; PD-L1, programmed death-ligand 1; RT, radiotherapy; T, tumour; TPeX, cisplatin/docetaxel/cetuximab.

patient population, especially as in some countries in Asia the EXTREME regimen is not reimbursed. Docetaxel, cisplatin and cetuximab (TPeX) (although the safety data are only available for induction therapy in Asian patients),[38] and paclitaxel and carboplatin plus cetuximab (PCE) which has shown promising activity in Japanese patients,[39] are alternative treatment options, and the wording of 'recommendation 3t' below was amended to reflect this with 100% consensus.

3r. **Every effort should be made to ensure that the administration of** post-operative RT or CRT starts within 6 weeks of surgery [II, A; **consensus = 100%]**.

3s. Pembrolizumab in combination with platinum/5-FU and pembrolizumab monotherapy are two approved regimens for patients with R/M SCCHN expressing PD-L1 (CPS $\geq$1) [I, A; ESMO-MCBS v1.1 score: 4]. **The choice of pembrolizumab monotherapy or chemotherapy plus pembrolizumab may be based on CPS, tumuor burden and symptoms [V, B; consensus = 100%].**

3t. Platinum/5-FU/cetuximab remains the standard therapy for patients with R/M SCCHN not expressing PD-L1 [I, A; ESMO-MCBS v1.1 score: 3].[34] **Pembrolizumab plus chemotherapy [II, C],** TPeX[40] **[II, B], and PCE [II, B] are** also treatment options in this population **[consensus = 100%]** (Figure 5).

3u. Nivolumab is both FDA- and EMA-approved for recurrent/metastatic patients who progress within 6 months of platinum therapy[41-43] [I, A; ESMO-MCBS v1.1 score: 4].

Table 2. Summary of applicability (availability) of drugs, equipment and testing according to Asian country

Drugs/equipment		CSCO	ISMPO	JSMO	KSMO	MOS	SSO	TOS
		Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N
Imaging	PET/PET/CT	Y	Y	Y	Y	Y	Y	Y
Assays	p16 IHC	Y	Y	Y	Y	Y	Y	Y
	HPV test such as DNA, RNA or ISH	Y	Y	N	Y	Y	Y	Y
	EBER	Y	Y	Y	Y	Y	Y	Y
	PD-L1 IHC	Y	Y	Y	Y	Y	Y	Y
	DPD testing	N	Y	N	N	N	Y	N
Radiotherapy	IMRT or VMAT	Y	Y	Y	Y	Y	Y	Y
Drugs	Pembrolizumab	Y	Y	Y	Y	Y	Y	Y
	Nivolumab	Y	Y	Y	Y	Y	Y	Y
	Cetuximab	Y	Y	Y	Y	Y	Y	Y

CSCO, Chinese Society of Clinical Oncology; CT, computed tomography; DNA, deoxyribonucleic acid; DPD, dihydropyrimidine dehydrogenase; EBER, Epstein—Barr-encoded RNA, HPV, human papilloma virus; IHC, immunohistochemistry; IMRT, intensity modulated radiotherapy; ISH, *in situ* hybridisation; ISMPO, Indian Society of Medical and Paediatric Oncology; JSMO, Japanese Society of Medical Oncology; KSMO, Korean Society of Medical Oncology; PET, positron emission tomography; PD-L1, programmed death-ligand 1; RNA, ribonucleic acid; SSO, Singapore Society of Oncology; TOS, Taiwan Oncology Society; VMAT, volumetric modulated arc therapy.

Table 3. ESMO-MCBS table for new therapies/indications in SCCHN

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[a]
Cetuximab plus cisplatin or carboplatin plus 5-FU	First-line treatment of patients with R/M SCCHN	Cetuximab in combination with cisplatin or carboplatin and 5-FU in the first-line treatment of patients with R/M SCCHN[34,45] Phase III NCT00122460	Cisplatin or carboplatin + 5-FU Median OS: 7.4 months	OS gain: 2.7 months	OS HR: 0.80 (0.64-0.99)	No QoL benefit observed	3 (Form 2a)
Nivolumab	Platinum-refractory R/M SCCHN	Trial of nivolumab versus therapy of investigator's choice in R/M platinum refractory SCCHN (CheckMate 141)[41,46] Phase III NCT02105636	Investigator's choice (methotrexate or cetuximab or docetaxel) Median OS: 5.1 months	OS gain: 2.4 months 2-year OS gain 10.9%	OS HR: 0.70 (0.51-0.96)	QoL benefit reported (exploratory outcome)[b] Reduced toxicity	4 (Form 2a)
Pembrolizumab[c]	Untreated locally incurable R/M SCCHN with CPS PD-L1 expression $\geq$1	Trial of pembrolizumab in the first-line treatment of R/M SCCHN (KEYNOTE-48)[33] Phase III NCT02358031	Cisplatin or carboplatin/5-FU/cetuximab Median OS: 10.3 months	OS gain: 2 months	OS HR: 0.78 (0.64-0.96)	QoL: pending Reduced toxicity	4 (Form 2a)
Pembrolizumab[c]	Untreated locally incurable R/M squamous cell carcinoma with CPS PD-L1 expression $\geq$20	Trial of pembrolizumab in the first-line treatment of R/M SCCHN (KEYNOTE-48)[33] Phase III NCT02358031	Cisplatin or carboplatin/5-FU/cetuximab Median OS: 10.7 months	OS gain: 4.2 months	OS HR: 0.61 (0.45-0.83)	QoL: pending Reduced toxicity	5[d] (Form 2a)
Pembrolizumab[c] plus cisplatin or carboplatin/5-FU	Untreated locally incurable R/M squamous cell carcinoma with CPS PD-L1 expression $\geq$1	Trial of pembrolizumab in the first-line treatment of R/M SCCHN (KEYNOTE-48)[33] Phase III NCT02358031	Cisplatin or carboplatin/5-FU/cetuximab Median OS: 10.4 months	OS gain: 3.2 months	OS HR: 0.65 (0.53-0.80)	QoL: pending	4 (Form 2a)
Pembrolizumab	Treatment of patients with R/M SCCHN after previous platinum-containing chemotherapy with PD-L1 CPS expression $\geq$1	Trial of pembrolizumab versus standard treatment in patients with R/M SCCHN (KEYNOTE-40)[47,48] Phase III NCT02252042	Standard of care (methotrexate, docetaxel or cetuximab) Median OS: 7.1 months	OS gain: 1.6 months	OS HR: 0.74 (0.58-0.93)	QoL benefit reported (exploratory outcome)[e] Reduced toxicity	3[f,g] (Form 2a)

CI, confidence interval; CPS, combined positive score; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; 5-FU, 5-fluorouracil; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; QoL, quality of life; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck.

[a] ESMO-MCBS version 1.1. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

[b] QoL exploratory endpoint, therefore, not creditable.

[c] Three-arm trial comparing chemotherapy plus cetuximab versus chemotherapy plus pembrolizumab versus pembrolizumab monotherapy.

[d] The licensed indication is for CPS PD-L1 expression $\geq$1. This score relates to a planned subgroup illustrating enhanced benefit among a subset of the approved cohort with CPS PD- L1 expression $\geq$20.

[e] QoL evaluated as exploratory endpoint (as distinct from primary or secondary endpoint) is not eligible for ESMO-MCBS grading.

[f] European Medicines Agency (EMA) approval is restricted to PD-L1 $\geq$50% tumour proportion score (TPS). PD-L1 $\geq$1 CPS was a secondary endpoint eligible for ESMO-MCBS scoring.

[g] EMA indication is restricted to recurrent or metastatic head and neck cancer with PD-L1 $\geq$50% TPS. This approval is based on an exploratory analysis with no adjustment for multiplicity in which the median OS control arm was 6.6 months, with a gain of 5.0 months HR 0.53 (95% CI 0.35-0.81). Although exploratory analyses can be the basis for hypothesis generation or conjecture or even licensing approvals by regulatory authorities, since they are exploratory (as distinct from primary or secondary endpoints), they are not eligible for grading using ESMO-MCBS.

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Deficiencies in the functioning of dihydropyrimidine dehydrogenase (DPD), the main enzyme involved in fluoropyrimidine metabolism, due to genetic polymorphisms, occur in 3%-5% of Western/European patients and can lead to lethal fluoropyrimidine toxicity.[44] Due to the low incidence of DPD deficiency in Asian patients, however, DPD genotyping and phenotyping is not carried out in routine daily practice in Asia, but is recommended for patients, who experience severe 5-FU toxicity during and after their first cycle of chemotherapy. The original 'recommendation 3v' below was thus revised completely, to the version in bold text and Table 1, to reflect this.

3v. DPD testing is recommended before initiating 5-FU.

3v. **According to the specific genetic profile of the Asian patient population, DPD genotyping or phenotyping may be considered before initiating fluoropyrimidine-based therapy [III, C; consensus = 100%].**

4. Follow-up—Recommendations 4a-c

4a. Clinical follow-up, including head and neck examination by flexible endoscopy, should be carried out every 2-3 months during the first 2 years, every 6 months for years 3-5 and annually thereafter [III, A].

4b. Imaging should be carried out if symptoms occur or in cases of abnormalities found at the clinical examination [III, A].

4c. FDG-PET/CT is recommended 3 months after CRT for patients with node-positive disease to assess the necessity of neck dissection [I, A].

Drug and testing availability

The drug and testing availability for each of the seven Asian countries is summarised in Table 2, and the ESMO-Magnitude of Clinical Benefit Scales (ESMO-MCBSs) for the different systemic therapy options for the treatment of SCCHN are presented in Table 3. Resource limitations are the most important barrier to offering optimal diagnosis and treatment to patients with SCCHN across the different Asian countries.

CONCLUSIONS

The recommendations listed in Table 1 can be considered to constitute the consensus Clinical Practice Guidelines for the treatment of patients with SSCHN (excluding nasopharyngeal cancer) in Asia, and are the result of voting by the Asian experts both before and during the virtual 'face-to-face' meeting hosted by KSMO, to adapt the recently published EHNS-ESMO-ESTRO Clinical Practice Guidelines.[23]

Following 'face-to-face' discussions during the virtual meeting, the revisions highlighted in bold text in Table 1 were made to the wording of the recent EHNS-ESMO-ESTRO Clinical Practice Guideline 'recommendations' initially identified in the pre-meeting survey as not having the agreement of all the Asian experts, and resulted in a **100% consensus,** being achieved for all the recommendations listed.

Despite these changes, these Pan-Asian adapted recommendations show high concordance with the original EHNS-ESMO-ESTRO Clinical Practice Guideline recommendations for the treatment of patients with SCCHN,[23] with the acceptance of each recommendation by each of the Asian experts based on the available scientific evidence independently of the approval and reimbursement status of certain drugs in their individual countries.

A summary of the availability of the recommended treatment modalities and recommended drugs, as of July 2021, is presented for each participating Asian country in Table 2 and will obviously impact on some of the disease and patient management strategies that can be adopted.

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