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Variation in reported incidence and treatment approaches in *de-novo* oligo-metastatic and oligo-recurrent non-nasopharyngeal head and neck cancers across the continents: subgroup analysis from a head and neck cancer international group (HNCIG) survey

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Short Communication

Abstract

Background: We performed a secondary analysis of a global survey conducted on *de-novo* Oligo-metastatic and Oligo-recurrent non-nasopharyngeal head and neck cancers (OM-HNC and OR-HNC) under the aegis of the Head and Neck Cancer International Group (HNCIG) to evaluate the current perceptions, incidence and treatment approaches across various continents.

Material and methods: An 18-item questionnaire was developed by the HNCIG Young Investigator Subcommittee and distributed electronically to experts across 24 cooperative groups worldwide. Three rounds of invitations were sent, and responses were analysed using SPSS v24.

Results: A total of 204 responses were obtained and the majority (86.8%) were from academic institutes, with similar representation from different continents. The major

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responses were primarily from Europe (59.8%), followed by Asia (26.5%). Most respondents (81.9%) reported <10% incidence of de-novo OM-HNC, with regional variation (16%–20% reporting >10%, mainly in Asia and Europe). Oligo-recurrence was encountered more frequently, with 28.9% reporting rates up to 20% and a minority reporting up to 30%. For de-novo OM-HNC, 64.7% favoured combining systemic therapy with local treatment to both primary and metastatic sites, which is consistent across all continents. For OR-HNC, though a combination of systemic therapy with metastasis-directed treatments (MDTs) was the most common approach across continents, up to one-third favoured MDT alone, especially in certain regions. Stereotactic body radiotherapy was the most frequently utilised MDT approach, used >50% of cases by 74.7% of respondents, with 18.7% using it exclusively.

Conclusion: This global survey highlights the variability in the incidence estimates and treatment approaches for OM-HNC and OR-HNC. While most clinicians endorse combining systemic therapy with MDT, a substantial minority consider MDT alone, reflecting ongoing uncertainty and the need for establishing evidence-based guidelines in the future.

Keywords: *global variation*, *head and neck cancer*, *de-novo oligo-metastasis*, *oligo-recurrent*, *survey*

Introduction

De-novo oligo-metastatic and oligo-recurrent head and neck cancers (OM-HNC and OR-HNC) are known to have a distinct biologic behaviour and possibly better prognosis. The incidence of OM-HNC is low. Up to 10%–20% of patients develop metastasis following definitive treatment; however, certain cohorts may be at an elevated risk, such as those with hypopharyngeal cancers (30%) [1–3]. There are no clear, well-defined guidelines for the definition and treatment of this unique subset of patients, apart from a few consensus statements and retrospective series [2, 4–6]. Herein, we present a secondary analysis of data from a survey conducted under the aegis of Head and Neck Cancer International Group (HNCIG) to understand global variations in the incidence and management of OM-HNC [7].

Materials and methods

A survey questionnaire was developed by the Young Investigator Subcommittee of the HNCIG, a global research collaborative comprising 24 HNC research cooperative groups. The survey was developed based on the available literature and challenges faced in clinical practice. An 18-item survey questionnaire was created using Google Forms. The complete sets of questions are provided in Table 1. The details of the development of the questionnaire have been published previously [7]. The survey was distributed via email to individuals identified as having the relevant expertise through the individual HNCIG member organisations. A total of three rounds of emails were sent: the initial invitation, a first reminder 3 months later and a second reminder 1 month before the survey closed. Data were analysed using Statistical Package for Social Sciences version v 24.0 (IBM Corp Armonk, IL, USA).

Results

A total of 204 responses were obtained with a response rate of 15.6% (204/1,307) and 59.8% (n = 122) responses were from Europe, 26.5% (n = 54) from Asia, 8.3% (n = 170) from North America, 3.9% (n = 8) from Australia and 1.5% (n = 3) from South America. The majority of respondents were from academic centers (86.8%, n = 177) and 62.7% (n = 128) had more than 10 years of practice experience. By continent, the proportion of respondents from academic institutions was similar: Asia (88.8%), North America (88.2%), Europe (85.2%), Australia (87.5%) and South America (66.6%).

Among the responders, there was no clear consensus on the definition of OM-HNC, but it included either the number of metastases (≤3 metastases selected by 48% of respondents) or their size (≤3 cm in 35.8%) or the number of affected organs (≤3 organs in 43.6%).

Table 1. Questions included for the survey.

No.	Context	Questions
1.	Burden of HNC	How many new cases of head and neck cancer present to your center annually?
2.	Definition	How do you define oligo-metastatic disease in your clinical practice using the following criteria? a. Number of lesions b. Number of affected organs c. size of the largest lesion.
For de-novo OM-HNC (Oligometastasis at diagnosis): Questions 3-8		
3.	Incidence	What percentage of your patients present with de-novo oligo-metastatic disease?
4.	Factors for treatment decision	How would you score the following factors to decide on the intent of treatment (radical versus palliative)? Performance status, Extent of disease, Site of distant metastasis, Biological entity (HPV status, oral cavity), Availability of expertise in metastasis-directed (local) therapy, Patient's choice/ affordability, Social support of the patient.
5.	Choice of T/t	If your intent of treatment is radical, then what would be your preferred choice of treatment?
6.	Choice of MDT	What is your preferred choice of metastasis directed therapy for lung only oligo-metastasis?
7.		What is your preferred choice of metastasis directed therapy for liver only oligo-metastasis?
8.		What is your preferred choice of metastasis directed therapy for bone only oligo-metastasis (not at immediate risk of fracture or no need of stabilization)?
For distant OR-HNC (Oligometastases developing later in the disease course in patients with loco-regionally controlled tumour: Questions 9-14		
9.	Incidence	What percentage of your patients present with oligo-recurrence after initial curative treatment?
10.	Deciding factor for T/t	How would you score the following factors to decide on the intent of treatment (radical versus palliative)? Performance status, Extent of disease, Site of distant metastasis, Disease free interval/disease kinetics, Biological entity (HPV status, oral cavity), Availability of expertise in metastasis-directed (local) therapy, Patient's choice/ affordability, Social support of the patient.
11.	DFI	What is the disease-free interval at which you consider treatment with radical intent?
12.	Choice of T/t Sequence	a. What would be your choice of treatment for oligo-recurrent disease? b. if you consider both local metastatic directed therapy and systemic therapy, particularly cytotoxic drugs, what would be your preferred sequence of treatment?
13.	Choice of MDT	What would be your choice of MDT for lung metastasis?
14.		What would be your choice of MDT for liver metastasis?
15.		What would be your choice of MDT for bone metastasis (not at immediate risk of fracture or no need of stabilization)?
For radiation oncologists only: questions 16-17		
16.	Radiation Dose/fraction	If you choose to treat oligometastasis with radiotherapy, what dose fractionation would you prefer? (Dose/number of fractions) A. Lung, B. Liver, C. Spine, d. Non-spine bone
17.	SBRT	In what percentage (%) of your patients do you prefer SBRT over palliative/conventional radiotherapy to treat oligo-metastasis?
18	Future study	Would you be interested in participating in a retrospective study on oligometastatic disease?

De-novo OM-HNC

The incidence of de-novo OM-HNC patients was reported to be below 10% in clinical practice by the majority of respondents (81.9%, *n* = 167). This low incidence was consistently reported by the majority of respondents across different continents, with 83.3% (*n* = 45) from Asia, 88.2% (*n* = 15) from North America, 100% (*n* = 3) from South America, 79.3% (*n* = 96) from Europe and 100% (*n* = 8) from Australia (Figure 1). A minority of respondents reported a higher incidence of de-novo OM-HNC (>10%), particularly those from Asia (16.6%, *n* = 9) and Europe (20.7%, *n* = 25).

When radical intent treatment is planned for OM-HNC, the majority (64.7%) of respondents preferred to combine systemic therapy with local therapy to both the primary and metastatic sites. This treatment approach was consistently endorsed across all continents (63% (34/54) Asia, 82.4% (14/17) North America, 66.7% (2/3) South America, 63.6% (77/121) Europe and 62.5% (5/8) Australia) (Figure 2). Only a few respondents (17.2%, *n* = 35) considered local therapy for the primary and metastasis-directed treatments (MDTs) without any systemic treatment, an approach more commonly endorsed by responders in Europe (21.5%, 26/121) and North America (17.6%, 3/17).

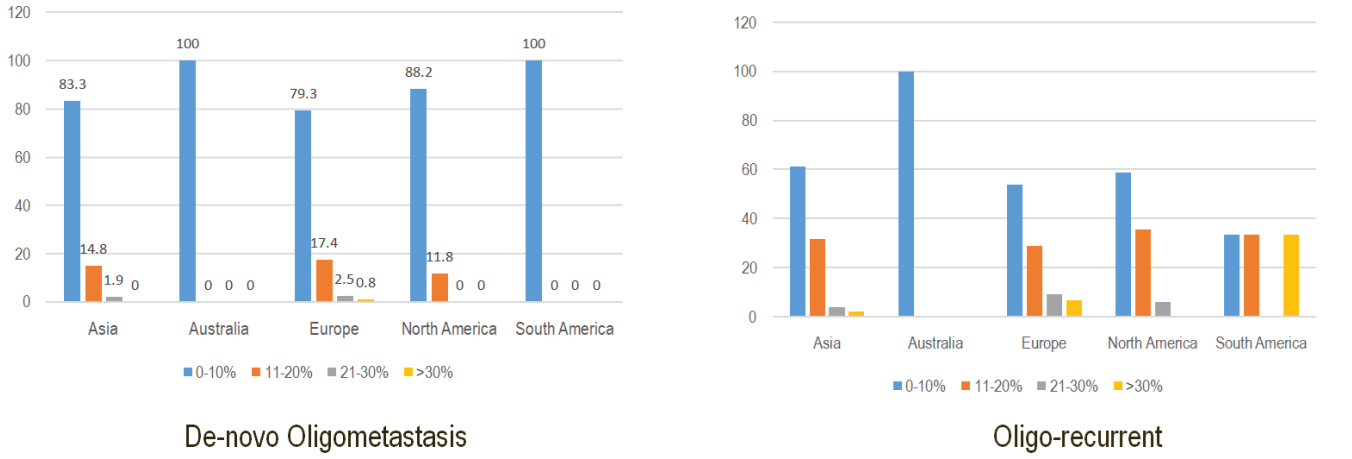

Figure 1. Incidence of de-novo OM-HNC and OR-HNC in clinical practice.

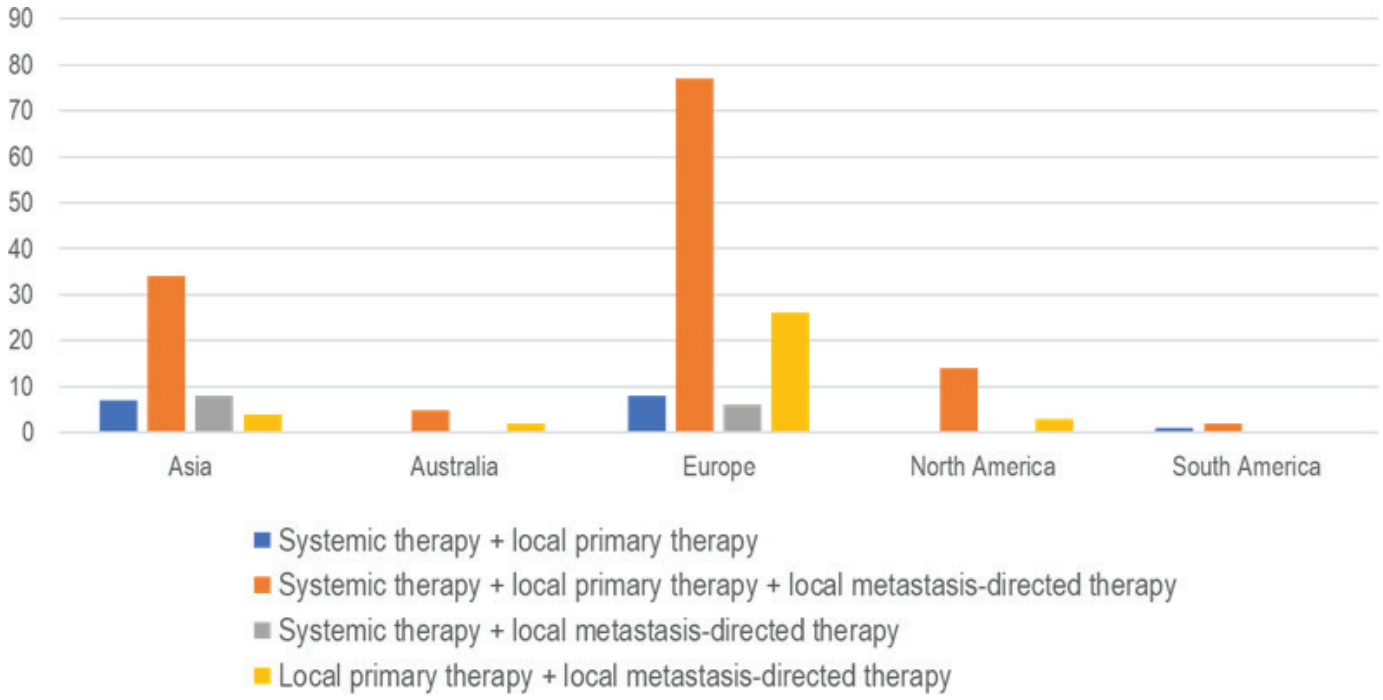

Figure 2. Treatment approaches to de-novo OM-HNC across continents.

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Distant OR-HNC

The majority of respondents (57.4%, *n* = 117) reported encountering oligo-recurrent disease in less than 10% of cases, while 28.9% (*n* = 59) reported rates of up to 20%. About one third of respondents from Asia (31.5%, *n* = 17), North America (35.3%, *n* = 6) and Europe (28.9%, *n* = 35) reported a higher incidence (11%–20%) of OR-HNC (Figure 1). Eleven (9.1%) respondents from Europe reported an incidence of up to 30% in their clinical practice.

Overall, in the case of oligo-recurrent disease following definitive curative treatment with a controlled primary site, the majority of respondents (63.7%, *n* = 130) would consider combining or sequencing both MDT and systemic treatment. The combination of systemic therapy with MDT was the most common approach across continents (Asia 68.5% (*n* = 37/54), North America 64.7% (*n* = 11/17), South America 100% (*n* = 3/3), Europe 62% (*n* = 75/121) and Australia 50% (*n* = 4/8)). However, a substantial minority of respondents from Australia (37.5%, *n* = 3/8), Europe (32.2%, *n* = 39/121), North America (23.5%, *n* = 4/17) and Asia (16.7%, *n* = 9/54) favoured MDT alone (Figure 3).

Stereotactic body radiotherapy (SBRT) was frequently favoured by radiation oncologists and clinical oncologists (*n* = 91) in delivering MDT. The majority (74.7%, *n* = 68) of respondents report frequent use of SBRT for MDT (>50% of their patients with OM-HNC), while 18.7% (*n* = 17) of respondents reported using SBRT exclusively. Finally, the majority of the respondents across all continents (Asia: 73.7%, *n* = 28; North America: 76.9%, *n* = 10; South America: 100%, *n* = 2; Europe: 91.7%, *n* = 99; Australia: 100%, *n* = 6) indicated a willingness to participate in a future retrospective, multinational study to provide a more objective understanding of the patterns of care and outcomes for patients with OM-HNC.

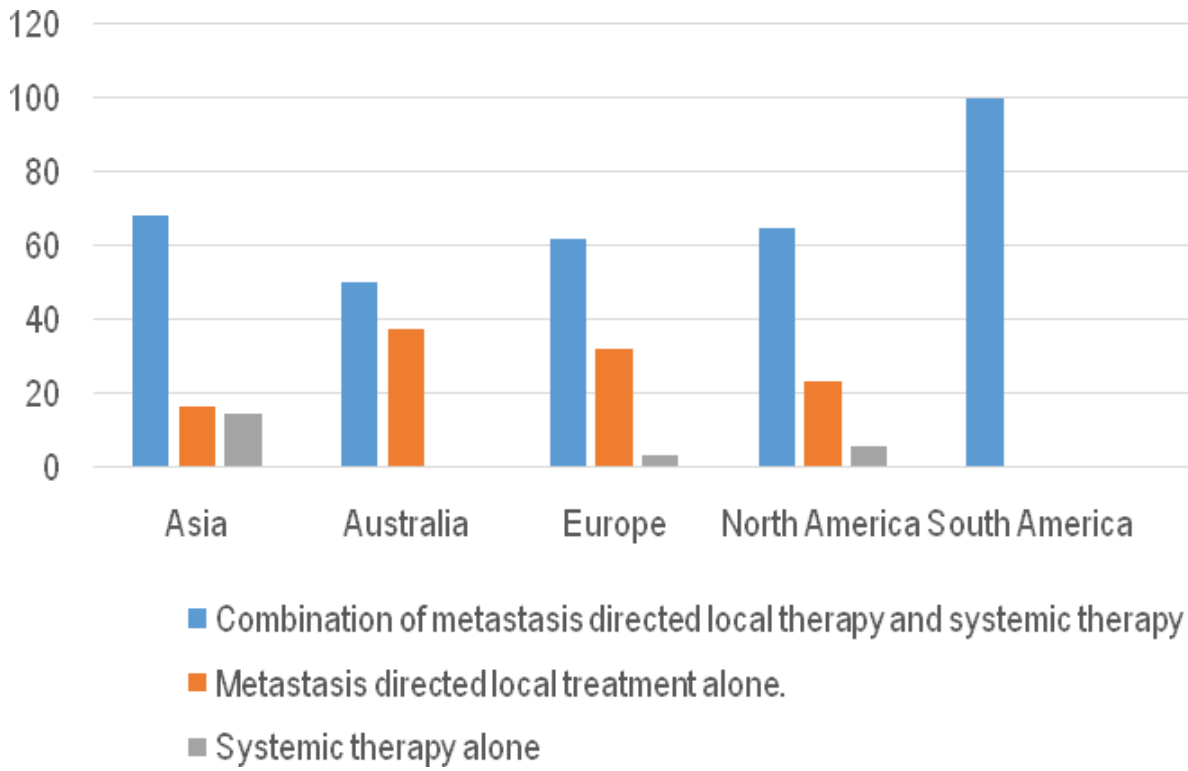

Figure 3. Treatment approaches to OR-HNC across continents.

Short Communication

Discussion

To the best of our knowledge, this is the first survey looking at the worldwide perception of incidence and overall practice patterns by continent in OM-HNC and OR-HNC. In this study, we have highlighted the reported incidence, as perceived by the respondents, and overall treatment approaches across different continents, although the responses were weighted towards Europe and Asia. There is a well-established body of literature highlighting significant differences in the presentation of primary head and neck tumours, their biologic behaviours and treatments rendered, with a significant divergence between Caucasians and Asians. The Asian population, especially the South Asian population, shows a higher incidence of oral cancer patients, largely attributed to prevalent risk factors such as betel quid and tobacco chewing, with a similar or better outcome compared to Caucasians, whereas HPV-positive oropharyngeal cancer is more prevalent among Caucasians with a better survival outcome [8–11]. Similarly, the treatment patterns vary with higher use of chemotherapy and radiotherapy among Asian populations and higher use of immunotherapy among Caucasian populations [12, 13], reflecting differences in healthcare infrastructure, approval timelines and clinical practice guidelines. These geographic and ethnic variations in disease presentation and management have prompted further exploration of the presentation and patterns of care in OM-HNC and OR-HNC within and among different continents.

The incidence of de-novo OM-HNC reported in the literature is low, and our finding is in line with what is reported in most publications [1]. In the questionnaire, the majority of respondents reported a self-estimated incidence of ≤10% in their clinical practice. However, the incidence of metachronous distant metastasis in the literature is reported to be higher [2, 3], and respondents from Europe and Asia more frequently reported an incidence of 10%–20%. One of the large studies by the DAHANCA group, which included 7,300 patients of larynx and pharynx cancers, reported a low incidence of de-novo metastasis of 3% and metachronous metastasis of 8%, though oligo-metastasis was not uniquely specified but would presumably be even lower [14]. A similar low incidence was also reported by other studies [15–17], suggesting the variations across different geographic regions. However, the DAHANCA study has reported the incidence of distant metastasis to be 21% in patients with p16 – positive oropharyngeal cancer [14].

Though the incidence of distant metastasis is increasing, the outcomes of metastatic head and neck cancers have improved only marginally over the years [18–20]. The reason may be that the 'one size fits all' approach has been applied, with all metastatic and recurrent diseases being treated together and with similar approaches. The concept of OM-HNC is being increasingly recognised in recent years, with many practitioners favouring a more radical approach for these patients. In recent years, the approach has changed towards incorporating high-intensity MDTs like radical surgery or radiotherapy into the management, which produce competitive overall survival (OS) results compared to standard systemic therapy alone (2 years OS 34.2% versus 20.6%, $p < 0.001$) [21]. There is evidence from national cancer registry studies, multicenter and single-center retrospective studies that local treatment of the primary in de-novo metastatic setting could lead to improved survival [21–24]. This evolution of use of local therapy to the primary is reflected in the current practice of the respondents, who indicated a preference for a combination of local and systemic therapy.

Though MDT in the form of surgery is well established, there is increasing evidence supporting the use of radiofrequency ablation, cryotherapy and especially SBRT in recent years for a more radical approach. Evidence supporting these approaches for OM-HNC and OR-HNC remains sparse; it is evolving and increasing [25–31]. The recent phase II randomised trial showed that SBRT alone achieved survival outcomes comparable to the EXTREME chemotherapy regimen combined with SBRT, while offering superior preservation of quality of life [32]. There are various ongoing studies evaluating the role of MDT exclusively for OM-HNC (NCT03283605, NCT03386357, NCT03070366, NCT05136768, NCT05815927 and NCT05721755) combining chemotherapy or immunotherapy with radiotherapy. These studies are expected to establish the appropriate treatment approach in the future.

Conclusion

There are perceived variations in the overall low incidence of OM-HNC and OR-HNC as reported by the respondents of various continents. Treatment approaches with more radical intent and deploying a combination of therapies remain the choice for the majority of respondents across all continents. The overwhelming willingness to collaborate in future multinational studies underscores the urgent need for harmonised definitions and prospective data to establish evidence-based guidelines for this unique subgroup of HNC patients.

Conflicts of interest

CH is the Co-Chair of the Young Investigators Committee of HNCIG.

AR reports personal fees and research grants from Novocure, and speaking fees from Merck Healthcare Germany outside the submitted work.

JB has done advisory boards for Castle Biosciences and Galera Therapeutics.

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HM is the Director and a shareholder of Warwickshire Head and Neck Clinic; Chair of the Head and HNCIG; and past president of the British Association of Head and Neck Oncologists. HM also reports receiving honoraria from AstraZeneca; Speakers Bureau on MSD, Sanofi Pasteur, Merck; Research funding from GSK Biologicals, MSD, Sanofi Pasteur, GSK Plc, AstraZeneca; travel accommodation expenses from Sanofi, Pasteur, MSD, Merck.

PS has had advisory relationships with Merck Serono, Servier, and MSD.

The rest of the authors do not have any conflicts of interest to declare.

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Author contributions

Study Concept and Design: MS, PS

Data Acquisition: MS

Data Analysis and Interpretation: All authors

Manuscript Preparation: MS, PS

Manuscript editing and review: All authors.

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