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Treatment patterns in older patients with locally advanced head and neck squamous cell carcinoma: Results from an EORTC led survey

1. Introduction

The number of patients with head and neck squamous cell carcinoma (HNSCC) is rising. Projections for the United States indicate an increase from approximately 50,000 to 67,000 (34%) HNSCC cases from the oral cavity, pharynx, and larynx between 2010 and 2030, while the population is expected to grow by 19% [1]. In 2010, 54% of these patients were predicted to be >65 years of age, whereas in 2030 the percentage of older HNSCC patients will probably increase to 66%. Unfortunately, the whole spectrum of older patients is underrepresented in clinical trials, and controversy exists on how patients with locally advanced HNSCC >70 years of age should be treated. A meta-analysis suggested that these patients do not benefit from addition of chemotherapy to radiotherapy [2]. This observation is likely explained by competing mortality and excess toxicity, especially from chemotherapy. Similarly, older patients do not seem to profit from altered fractionated radiotherapy, nor from addition of cetuximab [3,4]. However, in selected older patients with HNSCC, multimodality treatment can be safely delivered and results in similar outcome when compared to younger counterparts [5,6]. Geriatric assessment (GA) is recommended in older patients with cancer, but has not been validated for this purpose in HNSCC. Based on these controversies, we assumed that differences will exist in treatment delivered to selected older patients with HNSCC and in the use of GA. Furthermore, quality of life (QoL) can be severely affected by the cancer itself and by acute and late side effects from treatment. This may be even more pronounced in older patients. To investigate treatment patterns, use of GA and QoL assessment, a survey was done among European centers and selected centers outside Europe.

2. Materials and Methods

A 'Patterns of Care' survey was developed in mutual discussion with all authors and initially pilot-tested for refinement by specialists from different disciplines in the authors' centers. The survey addressed topics concerning treatment patterns in patients >70 years of age with LA-HNSCC involving oral cavity, oropharynx, larynx, and hypopharynx, as well as GA and QoL assessment (see Supplementary File S1).

An electronic communication with an invitation to participate in the survey was sent in 2018 to members of EORTC Head & Neck Group (HNG), Radiation Oncology Group (ROG), and Older Task Force (ETF).

Through the chairmen of the groups, the survey was also sent to members of Danish Head and Neck Cancer Group (DAHANCA), French Head and Neck Oncology and Radiotherapy Group (GORTEC), and European Head and Neck Society (EHNS). To characterize the responding participants' centers, it was asked whether the participants were working either in an academic center, community hospital, or private clinic, and what number of new older patients with HNSCC are evaluated per year, regardless of age. Based on this number, we classified centers into high volume (> 400 patients), intermediate volume (200–400 patients), and low volume (< 200 patients). In case of multiple respondents per single center, concordant answers were merged and reported as a single individual data. In case of discordant answers coming from different respondents from the same center, single answers were individually evaluated by first authors (SO, ID) and answers were selected only in case of unanimity between the two first authors. The results of the survey were analyzed using descriptive statistics and graphical displays produced with SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Respondents

Investigators from 111 institutions, representing 26 countries, returned the questionnaire (Table 1). The majority of the institutions were academic centers or national cancer centers ($n = 90$, 81.1%), followed by community hospitals ($n = 16$, 14.4%) and private clinics ($n = 5$, 4.5%). Eighteen institutions (16.2%) were high volume centers, 37 (33.3%) were intermediate, and 56 (50.5%) were low volume centers.

3.2. Treatment patterns

Almost one third of the institutions, never or hardly ever, (<5%) treat older patients with locally advanced oropharyngeal carcinoma with chemoradiotherapy, which is considered the standard of care for younger patients (see Fig. 1A and Supplementary Table S1). Another one third of the centers treat 5–20% of these patients with chemoradiotherapy, but investigators from 6 centers indicate that the >60% of their older patients with oropharyngeal cancer receive chemoradiotherapy. Very few centers use cetuximab frequently, which is also the case for surgery followed by postoperative radiotherapy.

Thirteen centers (11.7%) treat the majority of their older patients with locally advanced oropharyngeal cancer with radiotherapy alone. Twelve centers (10.8%) de-intensify treatment for older patients with HPV positive oropharyngeal cancer in comparison to older patients with HPV negative disease by either reducing radiotherapy dose or target volume, or a different choice with regard to systemic therapy.

For locally advanced laryngeal and hypopharyngeal carcinoma, treatment patterns are comparable to those for oropharyngeal

¹These authors contributed equally to this work and share first authorship

Table 1
Respondents by country.

Country	Institutions (n = 111) n (%)
UK	17 (15.3)
France	13 (11.7)
Germany	12 (10.8)
Italy	12 (10.8)
Netherlands	9 (8.1)
Belgium	8 (7.2)
Switzerland	7 (6.3)
Spain	5 (4.5)
Portugal	4 (3.6)
Egypt	3 (2.7)
Poland	3 (2.7)
Denmark	2 (1.8)
Israel	2 (1.8)
Turkey	2 (1.8)
Austria	1 (0.9)
Brazil	1 (0.9)
Croatia	1 (0.9)
Cyprus	1 (0.9)
Finland	1 (0.9)
Greece	1 (0.9)
Iceland	1 (0.9)
Japan	1 (0.9)
Norway	1 (0.9)
Slovenia	1 (0.9)
Sweden	1 (0.9)

carcinoma, including variability between centers (see Fig. 1B and C and Supplementary Tables S1 and S2).

For oral cavity cancer, investigators from 41 centers (36.9%) indicated that they treat at least half of their older patients with surgery

followed by postoperative radiotherapy, while chemoradiotherapy and radiotherapy with cetuximab is hardly used (see Fig. 1D and Supplementary Table S4). Investigators from three centers (2.7%) estimated that they treat at least half of these patients with radiotherapy alone.

For all tumor sites, most centers treat only a small minority of the patients with supportive care alone.

3.3. Treatment patterns by country

In the UK and especially in the Netherlands, older patients affected by locally advanced oropharyngeal cancer seldom receive chemoradiotherapy (Fig. S2). In the Netherlands and in a subset of UK centers, most patients are treated with radiotherapy alone, while in other UK centers mainly surgery with postoperative radiotherapy is used. A surgical approach is also often used in Germany and in a subset of Italian centers. Single centers in France and Italy indicate that >60% of these patients with oropharyngeal cancer are treated with radiotherapy plus cetuximab and one Belgian site uses cetuximab in about half of the patients.

For larynx cancer, treatment patterns by country resemble those for oropharyngeal cancer (Supplementary Fig. S1), although cetuximab is less frequently used.

Half of the centers in Germany treat 40–80% of older patients with locally advanced hypopharyngeal carcinoma with surgery followed by radiotherapy (RT), and this is similar for 40% of Italian centers. In other countries, mainly radiotherapy alone is used, followed by chemoradiotherapy (Supplementary Fig. S2).

For oral cavity cancer, a more homogenous picture is seen with surgery plus radiotherapy as preferred treatment in all countries. However, a few centers in Italy and in the Netherlands treat the majority of these patients with RT alone (Supplementary Fig. S3).

Fig. 1. Treatment patterns for older patients with locally advanced HNSCC.

3.4. Treatment patterns by volume

High volume centers tend to treat a smaller proportion of older patients with locally advanced oropharyngeal cancer with multimodal therapy compared to intermediate and low volume centers (Fig. S3). More than one half of high volume centers (55.6%) treat $\leq 5\%$ of these patients with chemoradiotherapy or surgery followed by radiotherapy while $>40\%$ of the patients get radiotherapy alone. However, two high volume centers (11.1%) indicate that they treat $>40\%$ of the patients with surgery plus postoperative radiotherapy. This is the case in 27.0% of intermediate volume centers and in 32.2% of low volume centers.

For larynx and hypopharynx carcinoma, treatments patterns do not appear to differ substantially according to center volume (Supplementary Fig. S4 and S5).

For oral cavity cancer, a reverse pattern compared to oropharyngeal cancer was found: surgery and postoperative radiotherapy is delivered to at least 60% of the patients in 55.5% of high volume centers, 32.4% of intermediate volume centers, and 33.9% of the small volume centers (Supplementary Fig. S6).

3.5. Treatment specification

On average, 55.4% (range 0–100%) of the patients who are treated with primary radiotherapy, with or without systemic treatment, are irradiated with conventional fractionation, while 6.5% (range 0–90%) is treated with hyperfractionated radiotherapy and 21.7% (range 0–96%) with accelerated radiotherapy. Only two centers (1.8%) indicated that they limit the radiotherapy target volume in older patients compared to guidelines (e.g. treat only gross tumor volume (GTV) with a margin). On average, 15.6% (range 0–50%) of the patients receive radiotherapy with palliative intent.

Of the patients who receive chemoradiotherapy, on average, 22.6% (range 0–100%) receive 3-weekly high dose cisplatin (80–100 mg/m²), whereas 30.7% (range 0–100%) are treated with weekly cisplatin 30–40 mg/m², 12.8% (range 0–100%) with weekly carboplatin, and 4.2% (range 0–60%) with 3-weekly carboplatin plus 5-fluorouracil. Other cytotoxic drugs that are used are mitomycin (especially in Germany), paclitaxel (one center) and capecitabine (one center). Also, for postoperative chemoradiotherapy there is a slight preference for weekly cisplatin (on average used in 34.7% of the patients) over 3-weekly high dose cisplatin (on average used in 26.9% of the patients). Twenty centers (18.0%) always arrange insertion of a percutaneous endoscopic gastrostomy (PEG) tube in older patients treated with chemoradiotherapy, while 62 centers (55.9%) do this in selected cases. Indications that were mentioned for PEG tube insertion were weight loss before start of treatment, concern about intake during treatment, dysphagia, tumor location, tumor volume, bilateral neck irradiation, and general condition.

With regards to surgery, advanced techniques are used in a substantial subset of older patients: on average 24.1% (range 0–95%) is operated with transoral laser or robot surgery and 36.0% (range 0–100%) with microvascular reconstruction. Limited surgery, compared to guidelines, is used on average in 16.4% (range 0–80%) of the patients.

3.6. Geriatric assessment

In fourteen centers (12.6%), GA is always performed in older patients with LA-HNSCC, while 43 centers (38.7%) never do GA and 39 centers (35.1%) do GA in selected cases. Information is missing for fifteen centers. The G8 and the Timed Up & Go Test are the most frequently used instruments and 32 centers (28.8%) offer comprehensive geriatric assessment (CGA) (see Table S2). Older patients with LA-HNSCC are always referred to a geriatric specialist in ten centers (9.0%), but this is never done in 48 centers (43.2%) and in selected cases in 38 centers (34.2%).

3.7. Treatment patterns by geriatric assessment

Analysis of treatment patterns in centers where GA is always performed in comparison to centers where GA is sometimes done or never done, did not reveal striking differences, except for hypopharyngeal cancer where centers that always perform GA are less likely to treat older patients with surgery and postoperative radiotherapy (Supplementary Fig. S7–S10).

3.8. Quality of life assessment

In 22 centers (19.8%), QoL is assessed on a routine basis, while 56 centers (50.5%) only assess QoL within studies and 18 centers (16.2%) never do. Information is missing for fifteen centers (13.5%). The EORTC QLQ-30 and the head and neck cancer specific modules EORTC-QLQ HN35/HN43 are the most frequently used instruments (Table S3).

4. Discussion

With this survey, we obtained a comprehensive overview of the patterns of practice regarding treatment of older patients with LA-HNSCC across Europe and beyond. According to our survey, only a very small percentage of older patients with a curable HNSCC are treated with a palliative intent. Significant areas of heterogeneity have nonetheless been demonstrated. In particular, a non-negligible percentage of older patients affected with LA-HNSCC receives chemoradiotherapy, and this differs between countries. Weekly cisplatin is the most used systemic regimen given concurrently with radiotherapy. Strengthening the notion cetuximab is not considered the standard of care in older patients. For radiotherapy, conventional fractionation and usual dose and treatment volumes, as adopted for the non-older population, are the most common chosen option. The use of surgery, in the context of a bimodal or trimodal approach, as curative treatment for patients with oropharyngeal cancer, presents a relevant heterogeneity across Europe. Surgery is commonly performed in countries like Germany and Italy, but seldom in Belgium and the Netherlands. Interestingly, high volume centers are less likely to use chemoradiotherapy as primary treatment when compared to intermediate and small volume centers. However, it should be noted that most high volume centers are located in the UK and the Netherlands. This heterogeneity reflects conflicting results in the literature about benefit from adding chemotherapy to radiotherapy in patients with LA-HNSCC >70 years. [2,5–8].

It is a common thought that, if treated irrespective of calendar age, fit older patients can derive a similar survival advantage as their younger counterparts. Therefore, undertreatment is suggested to be an important cause of the worse treatment outcomes observed in the older population with HNSCC. On the other hand, frail older patients are expected to derive far less benefit from a standard treatment approach and competing non-cancer mortality must be taken into account when approaching this category of patients. Geriatric assessment may help the clinician to select the best available treatment and tailor supportive care accordingly. As a geriatrician is not always available and CGA can be time-consuming, an array of assessment tools have been developed to act as surrogate [9]. Data from our survey depicts an extremely fragmented reality in terms of geriatric assessment and tools adopted, strengthening the need to reach a consensus regarding the context where a geriatric approach is warranted in the older population with HNSCC, and how this could be used to guide treatment decisions. Broadly addressing this issue, the ELAN-ONCOVAL (Elderly Head and Neck Cancer-Oncology Evaluation) study was conceived to determine a standard treatment for patients aged ≥ 70 years (NCT03614936). The trial enrolls patients with HNSCC >70 years who are not amenable to surgery and classifies those patients, using geriatric assessment, as fit or unfit. Preliminary results were recently presented: the geriatric assessment changed the treatment planned after oncological evaluation alone in 8% of cases, due to the addition or deletion of systemic therapy.

[10]. Finally, assessment of different domains of QoL before, during, and after treatment can be used to provide supportive interventions through the HNSCC journey [11]. This survey demonstrated that QoL assessment is performed on a routine basis in one out of five centers.

This study has several limitations. The high percentage of academic centers may indicate that responses are not fully representative of patterns of care delivered. Furthermore, respondents were asked to provide an estimate of their patterns of practice, even though they were encouraged to derive their data from a registry whenever possible. Finally, no discrimination was made in the questionnaire between fit, vulnerable, and frail older patients, nor between young-old (65–75 years), old-old (76–85 years), and oldest-old groups (>85 years) [12]. Finally, due to the design of the study, no comparison with treatment patterns in younger patients can be made.

5. Conclusions

Treatment of LA-HNSCC in older patients poses serious challenges due to the changing epidemiology and the need to balance treatment efficacy and toxicities. The heterogeneity between institutions and between countries in treatment patterns, geriatric assessment, and assessment of QoL indicates that there is an urgent need to develop a consensus-based guideline that can be used as the standard of care in daily practice and as a control arm in future studies.

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Authors Contribution

Study Concepts: SFO, ID, AL.
Study design: SFO, ID, ST, CS, SS, VG, AL.
Data acquisition: DS, CC.
Data analysis and interpretation: ID, SFO, CF.
Statistical Analysis: CF.
Manuscript preparation: ID, SFO.
Manuscript revision: all authors.

Declaration of Competing Interest

Dr. Oosting reports grants from Celldex, grants from Novartis, outside the submitted work; Dr. Singer reports personal fees from Pfizer, personal fees from Bristol-Myers Squibb, personal fees from Boehringer-Ingelheim, personal fees from Lilly, outside the submitted work; all other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jgo.2021.05.007>.

References

- [1] Smith BD, Smith GL, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol*. 2009;27:2758–65. <https://doi.org/10.1200/JCO.2008.20.8983>.
- [2] Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NH Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. 2009;92:4–14. <https://doi.org/10.1016/j.radonc.2009.06.011>.
- [3] Bonner JA, Harrari PM, Giral J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*. 2010;11:21–8.
- [4] Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. 2006;368:843–54. [https://doi.org/10.1016/S0140-6736\(06\)69121-6](https://doi.org/10.1016/S0140-6736(06)69121-6).
- [5] Moya VA, Chandramouleeswaran S, Zhao N, et al. Older patients with squamous cell carcinoma of the head and neck and the benefit of multimodality therapy. *Oncologist*. 2015;20:159–65. <https://doi.org/10.1634/theoncologist.2013-0325>.
- [6] Amini A, Jones BL, McDermott JD, et al. Survival outcomes with concurrent chemoradiation for older patients with locally advanced head and neck cancer according to the National Cancer Data Base. *Cancer*. 2016;122:1533–43. <https://doi.org/10.1002/cncr.29956>.
- [7] Kish JA, Zhang Q, Langer CJ, et al. The effect of age on outcome in prospective, phase III NRG oncology/RTOG trials of radiotherapy (XRT) +/- chemotherapy in locally advanced (LA) head and neck cancer (HNC). *J Clin Oncol*. 2015;33(Suppl; abstr 6003). https://doi.org/10.1200/jco.2015.33.15_suppl.6003.
- [8] VanderWalde NA, Meyer AM, Deal AM, et al. Effectiveness of chemoradiation for head and neck cancer in an older patient population. *Int J Radiat Oncol Biol Phys*. 2014;89:30–7. <https://doi.org/10.1016/j.ijrobp.2014.01.053>.
- [9] Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. *CA Cancer J Clin*. 2017;67:362–77. <https://doi.org/10.3322/caac.21406>.
- [10] Mertens C, Le Caer H, Ortholan C, et al. The ELAN-ONCOVAL (Older head and Neck cancer-Oncology eValuation) study: evaluation of the feasibility of a suited geriatric assessment for use by oncologists to classify patients as fit or unfit. *Ann Oncol*. 2017;28 Issue suppl_5, mdx374.007.
- [11] Rogers SN, Barber B. Using PROMs to guide patients and practitioners through the head and neck cancer journey. *Patient Relat Outcome Meas*. 2017;8:133–42. <https://doi.org/10.2147/PROM.S129012>.
- [12] Balducci L. Management of cancer in the older. *Oncology (Williston Park)*. 2006;20:135–43.

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