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Treatment of primary tumor in metastatic head and neck Carcinoma: A systematic review and Meta-Analysis

Fausto Petrelli [a,*], Luigi Lorini [b], Alberto Paderno [c,d], Daniela Carioli [e], Francesca Trevisan [f], Vincenzo Capriotti [g], Massimiliano Nardone [e], Cristina Gurizzan [b], Carlo Resteghini [b,d], Paolo Bossi [b,d]

[a] Oncology Unit, ASST Bergamo ovest, Treviglio, BG, Italy
[b] Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy
[c] ENT surgery department, IRCCS Humanitas Research Hospital, via Manzoni 56, Rozzano, Milan 20089, Italy
[d] Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, Pieve Emanuele, Milan 20072, Italy
[e] Otorhinolaryngology Unit, ASST Bergamo ovest, Treviglio, BG, Italy
[f] Radiotherapy Unit, ASST Bergamo ovest, Treviglio, BG, Italy
[g] Otorhinolaryngology Unit, Portogruaro Hospital, ULSS4 Veneto Orientale, Portugruaro, Italy

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ABSTRACT

Introduction: The treatment of primary tumors in metastatic squamous cell carcinoma of the head and neck (HNSCC) is a complex and debated issue. This study evaluates the impact of treating primary tumors on overall survival (OS) and progression-free survival (PFS) in metastatic HNSCC through a systematic review and *meta*-analysis, with a focus on identifying potential biases and limitations in the available evidence.

Materials and Methods: A comprehensive literature search was conducted in PubMed, EMBASE, and The Cochrane Library for studies published up to January 2024. Studies comparing systemic therapy alone to systemic therapy combined with locoregional therapy targeting the primary tumor, with or without neck nodes, were included. Eligible studies reported OS or PFS outcomes in stage IV HNSCC or nasopharyngeal cancers. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using random-effects models to account for study heterogeneity.

Results: The *meta*-analysis included 48 studies comprising 33,637 patients. Treating the primary tumor significantly improved OS (HR = 0.55; 95 % CI, 0.49–0.61; P < 0.01) and PFS (HR = 0.57; 95 % CI, 0.35–0.95; P = 0.03). However, significant heterogeneity was observed (I^2 = 86 %), reflecting variability in patient populations, treatment protocols, and study designs.

Conclusions: This *meta*-analysis suggests that treating the primary tumor in metastatic HNSCC may be associated with improved survival outcomes. However, these findings must be interpreted with caution due to significant limitations, including high heterogeneity, potential biases, and the predominance of retrospective studies.

Introduction

Recent research has extensively investigated treatment strategies for primary tumors in metastatic head and neck cancers (HNSCC), including squamous cell head and neck carcinoma (HNSCC) and nasopharyngeal carcinoma. These studies have explored various approaches, such as surgery, radiation therapy (RT), chemotherapy (CT), and targeted therapies. A comprehensive approach is crucial for managing primary tumors in metastatic HNSCC, aiming to improve survival rates, reduce tumor burden, alleviate symptoms, and enhance overall quality of life. HNSCC encompasses a diverse group of cancers originating in the mucosal surfaces of the head and neck, including the oral cavity, pharynx, and larynx. It is often diagnosed at a locally advanced stage, with a 10 % of patients presenting with distant metastases at the time of diagnosis. Treating metastatic HNSCC poses significant challenges due to its aggressive nature and the involvement of critical anatomical structures, which can complicate surgical and radiotherapeutic interventions. Some studies suggest that a combination of surgery for the

* Corresponding author at: Oncology Unit, Oncology Department, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047, Treviglio, BG, Italy.
E-mail address: faupe@libero.it (F. Petrelli).

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primary tumor and neck metastases, along with postoperative radiochemotherapy (RTCT), can offer substantial benefits for patients with operable advanced metastatic HNSCC. In cases where systemic therapy alone may be inadequate, aggressive locoregional radiation therapy directed at the primary tumor can be a crucial component of the initial treatment strategy. Early studies have underscored the need for further research, particularly through prospective clinical trials, to evaluate the impact of primary tumor ablation on survival outcomes in patients with distant metastases. These studies particularly highlight the importance of distinguishing between oligometastatic and polymetastatic disease, as the therapeutic benefit and prognosis may differ significantly between these subgroups [1–3].

The rationale for treating the primary tumor in metastatic HNSCC is based on several factors. First, the primary tumor can significantly contribute to morbidity, causing pain, obstruction, and functional impairments that can severely impact the patient's quality of life. Second, reducing the burden of the primary tumor may potentially decrease the overall tumor load, improving the efficacy of systemic therapies and reducing the risk of further metastatic spread. Cytoreductive surgery and targeted radiation therapy can play a vital role in eliminating primary tumors and limited metastatic deposits, reducing the immunosuppressive tumor burden, and enhancing adaptive immune responses [4]. Additionally, recent advancements in systemic therapies, such as immune checkpoint inhibitors and targeted agents, have shown promising results in managing metastatic HNSCC. These therapies enhance the body's immune response against cancer cells or inhibit specific pathways crucial for tumor growth and survival. Integrating these systemic therapies with locoregional treatments could potentially maximize therapeutic effectiveness while minimizing the traditional side effects of CT.

This systematic review and *meta*-analysis aim to consolidate findings from various studies to better understand the efficacy of different treatment modalities for primary tumors in metastatic HNSCC, with a specific focus on RT-based approaches. By synthesizing data from multiple sources, this study seeks to provide a clearer understanding of the benefits and potential drawbacks of treating the primary tumor in the context of metastatic disease.

Material and methods

This review was designed and developed according to the PRISMA guidelines.

Search strategy and inclusion criteria

We utilized the PICOS (Participants, Interventions, Comparators, Outcomes, and Study Design) approach to formulate a key issue, which served as the basis for our literature search. We searched the PubMed, EMBASE, and The Cochrane Library databases using the following terms: (*laryngeal or larynx or oral or pharynx or pharyngeal or head and neck or nasopharynx or nasopharyngeal) and (cancer or carcinoma) and (metastatic or stage IV or advanced) and (treatment or local therapy or primary tumor or local control or locoregional therapy or radiotherapy or surgery or chemoradiotherapy or radiochemotherapy or chemoradiation or CTRT or RTCT or CRT) and survival*. We included all entries up until January 2024.

After identifying relevant studies based on their titles and abstracts, we conducted a two-step screening process using specific exclusion and inclusion criteria. The first step involved excluding titles and abstracts that were clearly irrelevant and retaining those that potentially addressed the research question. In the second step, we performed full-text screening on the retained articles. Publications were included in our study sample if they met the following criteria: 1) they were published in English and available in full text, 2) they were prospective randomized or retrospective studies comparing systemic therapy alone with systemic therapy plus (upfront or consolidation) locoregional therapy to the primary tumor (including both cohort studies and retrospective case-control studies), 3) the participants were limited to those with stage IV HNSCCs comprising also nasopharyngeal cancers, and 4) the study outcomes included patient survival or recurrence.

We excluded papers where treatment of the primary tumor was offered at the diagnosis of localized or locally advanced non metastatic tumors, and the tumor later recurred with distant metastases. Moreover, in cases where multiple publications were from the same group, we only included studies that reported data from non-overlapping time periods.

Data extraction and quality of trials

Three authors collected data independently by using a data extraction template, with a fourth senior editor (PB) serving as a tiebreaker when consensus was not reached. For each study, the information collected included median follow up, number of patients, primary site, type of study, treatment (with particular attention given to those offered to treat the primary tumor), dose of RT, type of systemic therapy, clinical outcome in terms of overall survival (OS) and progression-free survival (PFS). We assessed the methodological quality of the observational studies using the Newcastle–Ottawa Scale (NOS), a tool commonly used in evidence-based healthcare to evaluate the quality of non-randomized studies, especially cohort and case-control studies. A score of at least 7 indicates higher quality evidence and a lower risk of bias, while lower scores suggest moderate to poor quality studies.

Statistical analysis

The primary endpoint was OS with PFS as the secondary endpoint. HRs were pooled for survival analysis to provide an aggregate prognostic value of treatment to the primary cancer, incorporating HRs with 95 % CIs from multivariate or univariate analyses available in the included studies. Sensitivity analysis was conducted even with *meta*-regression based on participant ethnicity (Asian vs. non-Asian), subsite and histology (nasopharyngeal vs squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx), median follow-up ($\geq$vs $<$ 3 years), manuscript quality (high vs. moderate), and study design (retrospective vs. prospective). Heterogeneity among studies was assessed using Cochran's Q test, with $P < 0.05$ or $I2 > 50$ % indicating significant heterogeneity, in which case a random-effects model (Der Simonian-Laird method) was applied. Otherwise, a fixed effects model was used. HR < 1 indicated improved survival in patients undergoing resection of liver metastases. Prediction intervals were also calculated. We finally investigated the publication bias for OS *meta*-analyses with a visual inspection of funnel plots and with the Begg's and Egger's bias test. Moreover, in the presence of publication bias for the primary analysis, we conducted a trim and fill adjusted analysis to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size. Data were analyzed using the Review Manager (RevMan) software, version 5.4, The Cochrane Collaboration, 2020.

Results

Literature search

The primary search retrieved 2060 articles. Once we identified the relevant studies through title and abstract information and removed duplicates, 73 studies were selected for full-text evaluation. Of these, 48 met the requirements and were included in the systematic review for a total of n = 33,637 patients [2,3,5–49]. The PRISMA search flow diagram is presented in Fig. 1. Twenty-nine studies included only nasopharyngeal cancer patients, the remaining included patients with different HNSCC subsites. Thirty trials included Asiatic patients, the remaining Western countries subjects (mainly from United States).

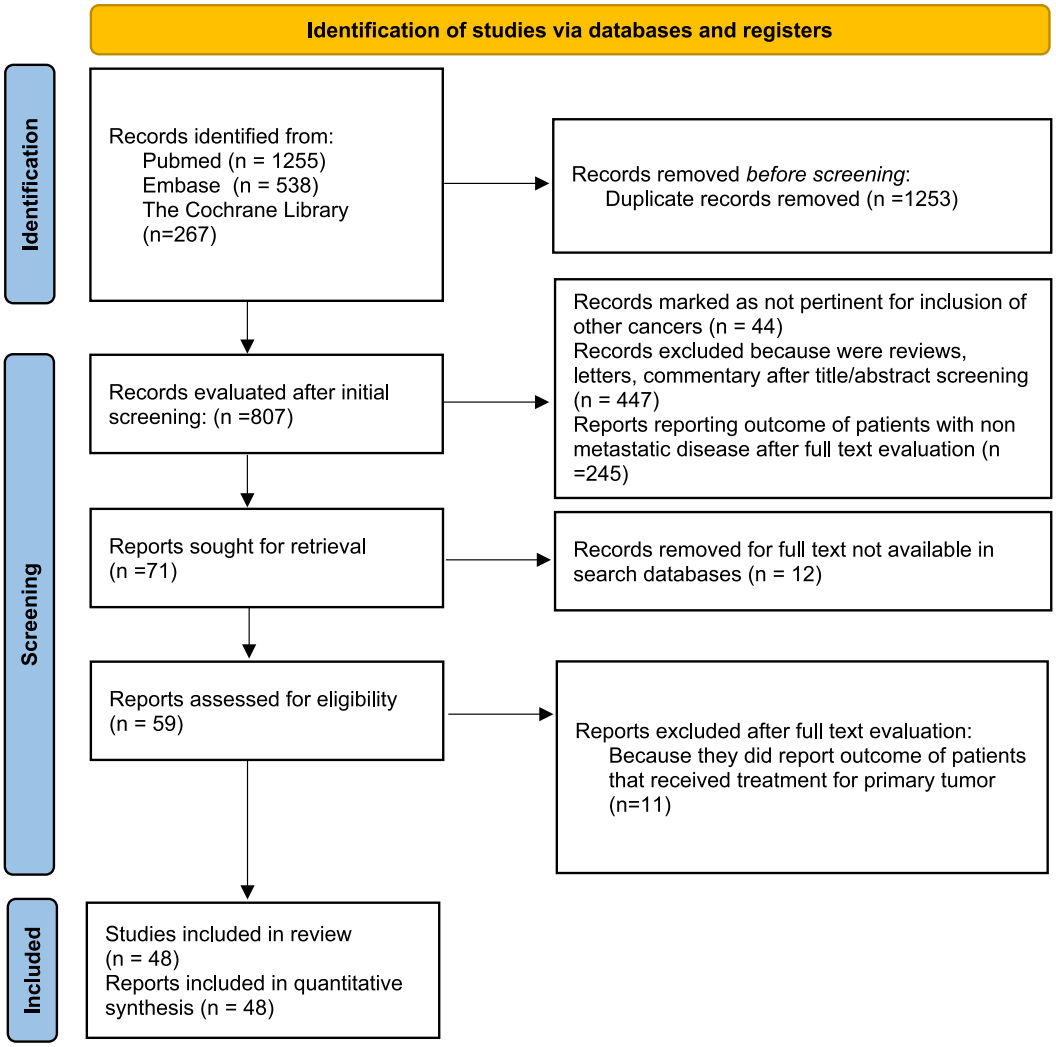

Fig. 1. Flow diagram of included studies.

Most papers were retrospective in nature except one randomized phase III trial. The overall study period ranged from 2006 to 2023. Most patients received systemic chemotherapy (CT) plus or minus targeted agents and treatment to the primary tumour (either standard or reduced dose RT or surgery). A minority received also local therapy for distant metastases (mainly bone metastases). All studies except n = 1 included a mixed population of poly and oligometastatic cancers. Only 3.6 % of the individuals exhibited metachronous metastases, while the remainder presented with de novo metastatic disease.

The main characteristics and intervention details of the selected studies are reported in Table 1. Mean NOS score was 5.9 (range 5–9). Nine studies were of high quality (NOS score 7–9), n = 39 of moderate quality. Overall, all of the included studies were of sufficient to high quality.

Overall survival

Among n = 42 studies with data available, treating the primary tumour in addition to systemic therapies improved largely OS (Fig. 2) with an HR of 0.55 (95 %CI 0.49–0.61; P < 0.01). heterogeneity was high (I^2 = 86 % so a random effect model was used). The prediction interval was 0.29–0.94.

Progression-free survival

Among n = 5 studies with data available PFS was improved with treatment of primary tumour in addition to systemic agents (HR = 0.57, 95 %CI 0.35–0.95; P = 0.03; Fig.3).

Publication bias

Evidence of publication bias was observed (Fig.4). Both Begg's test (P = 0.003) and Egger's test (P = 0.02) yielded significant results. The Trim and Fill method, which accounts for missing studies using a random effects model, indicated that there are 5 missing studies located to the left side of the mean effect. Based on these parameters, the method suggests a point estimate and 95 % confidence interval of 0.49 (95 %CI 0.44–0.54) for the combined studies using Trim and Fill.

Subgroup analysis

The effect of treatment on the primary tumour was more pronounced in nasopharyngeal cancers (HR = 0.47, 95 %CI 0.39–0.57; P < 0.01) compared to other sites (HR = 0.62, 95 %CI 0.55–0.7; P < 0.02; Fig.2), and this difference was highly significant (P < 0.01). The effect size remained consistent in studies with more than and less than 3 years of follow-up (HR = 0.54, 95 %CI 0.46–0.65 and HR = 0.51, 95 %CI 0.46–0.57, respectively). Furthermore, the effect was more prominent in

Table 1

Author/ year	Type of study	Country	N° pts	Median follow up (months)	Primary subsite (%)	Type of treatment of primary tumor	Dose of RT	Treatment for metastases	NOS score
Borson/ 2022	Retrospective series	US	40	–	OPC (52.5 %), hypo/ larynx (40 %); OC (7.5 %)	Surgery (55 %); CTRT (45 %)	–	CT (100 %); ICIs 27.5 %. Local therapy for M + 45 %:	5
Carey/2023	Retrospective analysis of the NCDB database	US	627	–	OPC (100 %)	Surgery (6 %); RT (33 %)	RT >= 60 Gy	CT (100 %); ICIs (12 %)	5
Hori/2019	Retrospective series	Japan	93	8.44	Pharynx (48.4 %), OC (16.1 %), larynx (6.5 %), salivary glands (6.5 %), nasal cavity and paranasal sinus (10.8 %), thyroid gland (2.2 %), external auditory canal (3.2 %) and unknown sites (8.6 %)	RT (74 %); Surgery (25.3 %)	–	–	5
Kabarriti/ 2018	Retrospective analysis of the NCDB database	US	2198	11.9	OC (11 %); OPC (45 %); NPC (11 %); hypo (15 %); larynx (17 %), salivary glands (2 %)	RT (1099)	60 Gy in 30 fractions (BED 72 Gy10)	CT (100 %); ICIs (2 %)	6
Liu/2023	Retrospective analysis of SEER database	US	218	NR	Larynx (100)	Surgery (50 %), RT (65 %)	–	CT (58 %)	5
Nguy/2021	Retrospective analysis of the NCDB database	US	556	17.5	OPC HPV+ (100 %)	RT (57 %)	RT>= 72 Gy	CT (98 %), NA 3 %; ICIs (13 %)	6
Omata/ 2023	Retrospective series	Japan	98	9	OC 8 %; Nasal sinus 10 %; Nasopharynx 4 % OPC 23 %; Hypo 44 % Larynx 10 %	RT or CTRT (42 %)	30–60 Gy (6 %); 60–70 Gy (36 %)	RT (14 %), surgery (1 %); ICIs +- CT (18 %), CT (69 %)	6
Pan/2019	Retrospective analysis of SEER database	US	446	12–60	Larynx (100)	Surgery (10 %)	–	NR	5
Patel/2016	Retrospective series (SEER database)	US	6663	–	OPC 2329 (35 %); larynx 1510 (22.7 %); OC 1088 (16.3 %); hypo 862 (12.9 %); NPC 483 (7.2 %); major salivary glands 174 (2.6 %); nasal cavity and paranasal sinuses 172 (2.6 %); thyroid gland 35 (0.5 %); other sites 10 (0.2 %)	RT (42.2 %); Surgery (9.8 %); surgery + RT (19 %)	–	CT	5
Rambeau/ 2019	Retrospective series	France	65	12.3	OC: 6 (9.2 %); OPC 26 (40 %); hypo 19 (29.2 %); larynx 6 (9.2 %); unknown 8 (12.3 %)	RT (100 %)	Radical (>= 60 Gy): 28 (68 %); Palliative (<60 Gy) 13 (20 %)	CT	6
Schwam/ 2015	Retrospective analysis of the NCDB database	US	2525	8.1	OC 15 %, OPC 35 %, NPC 10 %, Hypo 13 %, Larynx 27 %	Local therapy + systemic therapy 39.2 % (95.4 % RT, 12.3 % surgery); Local therapy only 19 %	–	CT (17.8 %)	6
Tang/2023	Retrospective series	France	148	11.8	OC 9 %, OPC 41 %, hypo 36 %, larynx 14 %	Surgery 6 %, RT or CTRT 94 %.	RT dose equal to 70 Gy (IMRT)	CT (100 %)	6
Wang W/ 2022	Retrospective analysis of SEER database	US	463	NR	Hypol (100 %)	RT or surgery (47 %)	–	CT (100 %)	5
Wang/2021	Retrospective series (SEER database)	China	735	19	OPC 75 %, NPC 14 %, hypo 11 %	Radical local treatment (e.g. CTRT) 57 %	–	CT (29 %)	6
Wang/2022	Retrospective Series (SEER database)	China	333	–	Non-OPC (100 %)	Surgery (9.3 %), RT (73 %)	–	CT (55 %)	5
Zhou/2021	Retrospective Series (SEER database)	China	303	15	OPC 89 %, hypo 11 %	CTRT 60 %; Surgery + CT 4 % RT + Surgery + CT 10 %	–	CT (100 %)	6
Zhu/2023	Retrospective series (SEER database)	US	3215	–	OC (NR), OPC (NR), Hypo (NR), larynx (NR)	Surgery (18 %)	–	–	5

(*continued on next page*)

Table 1 (*continued*)

Author/ year	Type of study	Country	N° pts	Median follow up (months)	Primary subsite (%)	Type of treatment of primary tumor	Dose of RT	Treatment for metastases	NOS score
Zumsteg/ 2017	Retrospective analysis of the NCDB database	US	3269	51.5	NPC 295 (9 %); OPC (41.1 %); OC 350 (10.7 %); larynx 836 (25.6 %); hypo 446 (13.6 %)	Low-intensity local treatment 19.9 %; High intensity local treatment 45.7 %*	High-intensity: >= 60 Gy; Low-intensity: < 60 Gy	CT (100 %)	8
Cao/2011	Retrospectve	China	221	NR	NPC (100)	RT on T and N (100 %) + CT	66–70 Gy IMRT	CT (64.3 %); CTRT (35.7 %)	5
Chen/2013	Retrospective	China	408	19.2	NPC (100)	RT on T and N (52.4 %)	90.7 % 2D, 9.3 % IMRT 70–74 Gy	CT (84.5 %); RT or surgery (% NA)	6
Chen/2018	Retrospective study	China	276	Up to 200	NPC (100)	RT on T and N	NR (2D, 3D or IMRT)	RT or surgery for bone metastases	8
Hu/ 2017	Retrospective analysis of SEER database	China	679	13	NPC (100)	RT on T and N (66 %)	–	–	6
Hu/2023	Retrospective series	China	163	22	NPC (100)	RT on T and N	NR (IMRT)	CT + ICIs (100)	5
Huang/ 2020	Retrospectiveseries	China	821	22.4	NPC (100)	RT on T and N (61 %)	NR (2D CRT, 3D CRT, IMRT)	CT (95.7 %) RT (16.6 %); Ablation (1.1 %) Intervational embolic (0.6 %); surgery (1.0 %)	6
Liao/2020	Retrospective series	China	150	23.7	NPC (100)	RT on T and N (78.0 %)	66–67 Gy (51.3 %) IMRT 71–74 Gy (48.7 %) IMRT	CT (100 %); RT (25.3 %); TACE (0.6 %); Surgery (0.6 %)	6
Lu/2023	Retrospective series	China	504	51	NPC (100)	RT on T and N (57 %)	66–70 Gy (IMRT)	CT (100 %) → ICIs; RT or surgery (20 %)	8
Nong/2019	Retrospective series	China	58	NR	NPC (100)	RT on T and N	70–72 Gy (IMRT)	CT + CTRT (100)	5
Rusthoven/ 2017	Retrospective analysis of the NCDB database	US	718	52.8	NPC (100)	RT on T and N (60.9 %)	< 30 Gy 4.0 % 30–49.9 Gy 19 % 50–69.9 Gy 19 % > 70 Gy 24 %	CT (100 %)	8
Shen 2015	Retrospective series	China	312	NR	NPC (100)	RT on T and N	NR	CT (60.3 %) RT (6.4 %); CTRT (63.3 %)	5
Sun XS/ 2020	Retrospective	China	502	44.9	NPC (100)	RT on T and N (61 %)	66–70 Gy IMRT or 2D	CT (100 %)	8
SunXS/ 2019	Retrospective	China	451	27.7	NPC (100)	RT on T and N (68.3 %)	–	CT (100 %)	6
SunXS/ 2019	Retrospective	China	226	33.9	NPC (100)	RT on T and N (69.5 %)	68–70 Gy on T and N, 30–40 Gy on bone M + . Technique: IMRT or 2D	CT (100 %); RT on bone M+ (30.1 %)	7
Tian/2015	Retrospective	China	263	25	NPC (100)	RT on T and N (60.8 %), in pts with response after ct or symptoms control	Median 70 Gy IMRT/3D	CT (89.1 %); RT (24.3 %)	6
Toumi/ 2022	Retrospective	Tunisia	112	10	NPC (100)	RT on T and N (23.0 %)	–	CT (77.7 %); RT (23.1 %)	6
Verma/ 2017	Retrospective	US	555	25.8	NPC (100)	RT on T and N (47 %)	≥ 60 Gy	CT (100 %)	6
Wang/2021	Retrospective	China	191	21.5	NPC (100)	RT on T and N (78 %)	Median 70 Gy: 77.2 % IMRT, 22.8 % 3D-RT	CT (100 %); RF/RT (23 %)	6
Xu/2020	Retrospective analysis of SEER database	US	224	NR	NPC (100)	RT (61 %)	–	CT (84 %)	5
Xu/2021	Retrospective	China	168	NR	NPC (100)	RT on T and N (86 %)	IMRT (66–70 Gy)	CT (100 %), other (31.5 %)	5
Yang /2022	Retrospective series	China	440	23	NPC (100)	RT on T and N ± CT (TOT 59 %, 53 % + CT, 6 % no CT)	66–70 (IMRT)	CT (100 %), ICI (41 %)	6
Yang YH/ 2021	Retrospective series	China	498	NR	NPC (100)	RT on T and N (62 %)	68–70 Gy (2DRT or IMRT)	CT (100 %)	5
Yang/2021	Retrospective	China	84	NR	NPC (100)	RT on T and N (70 %)	IMRT 59–69 Gy	CT (100 %), other (37 %)	5
Yao Y/2023	Retrospective series	China	462	94.9	NPC (100)	RT on T and N (56 %)	66–72 Gy (IMRT)	CT (100 %)	9
Yeh/2006	Retrospective series	Taiwan	125	NR	NPC (100)	RT on T and N	66–75 Gy (brachytherapy in n = 10 pts)	CT (31 %) or RT (46 %)	5

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Table 1 (*continued*)

Author/ year	Type of study	Country	N° pts	Median follow up (months)	Primary subsite (%)	Type of treatment of primary tumor	Dose of RT	Treatment for metastases	NOS score
You/2020	Randomized phase III	China	126	24	NPC (100)	RT on T and N (50 %)	IMRT (median 70 Gy)	CT (100 %)	6
Zeng/2014	Retrospective	China	234	22	NPC (100)	RT on T and N (59.8 %)	Median 70 Gy 82.9 % "conventional techniques" 14.3 % IMRT 2.8 % 3D −CRT	CT (100 %)	6
Zeng/2021	Retrospective	China	168	44	NPC (100)	RT on T and N (64.9 %)	IMRT (median 70 Gy, 9 % < 60 Gy)	CT (100 %), RT (30.3 % of who recieved RT on T and N, 0 % of who did non recieve RT)Surgery and hyperthermia (% NA)	7
Zhang/ 2022	Retrospective	China	2041	43.4	NPC (100)	RT on T and N (91.7 %)	Median 70 Gy	Various systemic agents (100 %) + local therapy on M+ (31 %)°	7
Zou/2017	Retrospective	China	462	NR	NPC (100)	RT on T and N (54.5 %)	2D or IMRT 68–70 Gy	CT (100 %), RT (20.4 %)	5

ICI, immune checkpoint inhbitors; CT, chemotherapy; RT, radiotherapy; CTRT, chemoradiotherapy; NPC, nasopharynx cancer; OPC, oropharynx cancer; OC, oral cavity cancer; hypo, hypopharynx cancer; RF, radiofrequency ablation.

* high-intensity local therapy was defined as 1) the receipt of a cumulative radiation dose to the head and neck ≥ 60 Gy, 2) oncologic surgery to the primary site, such as pharyngectomy, subtotal or total laryngectomy, or partial, hemi-, or total glossectomy, or 3) both. Lower intensity local therapy was defined as radiation to the head and neck at doses < 60 Gy or more limited surgical procedures, such as local tumor destruction, local tumor excision, biopsy, cryosurgery, electrocautery, photodynamic therapy, or laser ablation, unless head and neck radiotherapy to doses ≥ 60 Gy was also delivered.

° Surgery, radiotherapy, radiofrequency ablation, and particle implantation

Asiatic studies (HR = 0.47, 95 %CI 0.41–0.55; P < 0.01) compared to studies conducted in Western countries (HR = 0.58, 95 %CI 0.51–0.66; P < 0.01), but this it seems driven by frequent Asiatic nasopharyngeal cancers. Studies with higher NOS scores showed a reduced treatment benefit (HR = 0.62, 95 %CI 0.5–0.76; P < 0.01) compared to studies with moderate quality (HR = 0.56, 95 %CI 0.48–0.65; P < 0.01). As only one study had a prospective design, subgroup analysis was not conducted based on the type of study.

Discussion

The management of primary tumors and lymph nodes in individuals with metastatic HNC presents a significant challenge in the field of oncology. The primary objective is to improve survival rates and enhance the well-being of affected patients. This *meta*-analysis examines the effectiveness of various treatment strategies, focusing on RT and surgical interventions in stage IV disease and their impact on OS and PFS. A total of 47 studies involving 33,637 patients were included in this *meta*-analysis. The major finding of this study indicates that treating both the primary tumor and neck nodes leads to a significant improvement in both OS and PFS for patients diagnosed with metastatic HNC. The combined HR for OS was calculated to be 0.55, indicating a 45 % reduction in the risk of mortality when the primary tumor and nodes are managed along with systemic therapy. Similarly, the HR for PFS was 0.57, suggesting a considerable advantage in controlling disease progression, despite fewer studies including this outcome measure. These results emphasize the importance of an integrated treatment approach that combines local interventions with systemic therapies. Surgical or radiotherapeutic approaches are the main locoregional interventions in such cases. Even in the context of metastatic disease, surgical removal of the primary tumor can yield substantial benefits. In other types of cancer, cytoreductive surgery, aimed at removing as much of the tumor mass as possible, not only reduces tumor burden but also improves symptoms and potentially prevents further metastasis [50–52]. This is particularly significant in cases of HNSCC, where the primary tumor can significantly impact functions such as swallowing, breathing, and speech. Studies, including those conducted by Bell et al. [4], have indicated that surgery in combination with immunotherapy can enhance the body's immune response against residual tumor cells, resulting in improved outcomes. Radiotherapy also plays a crucial role in managing the primary tumor in metastatic HNSCC. Advances in RT techniques, such as stereotactic body RT (SBRT), allow for precise targeting of the tumor, enabling the delivery of high doses of radiation while minimizing damage to surrounding healthy tissues [53]. This precision reduces side effects and enhances treatment efficacy, allowing for uninterrupted systemic therapy. Consequently, when combined with systemic therapy, high-intensity local treatments can significantly improve survival rates [3]. The effectiveness of combining chemotherapy with radiation for locoregional disease even in the context of metastatic HNSCCC needs to be further validated through clinical trials. Unfortunately, there is limited evidence from randomized studies. The only phase III trial conducted by You et al [13]. examines the efficacy and safety of combining locoregional radiation therapy concurrent with chemotherapy alone in individuals with de novo metastatic nasopharyngeal carcinoma who responded well to initial chemotherapy.

The study provides compelling evidence that the addition of locoregional radiation therapy significantly improves OS and PFS in patients with chemotherapy-sensitive de novo metastatic nasopharyngeal carcinoma. The researchers concluded that this combined treatment should be considered the new standard of care for this specific patient population. This variation may be attributed to nasopharyngeal cancer's distinct biological characteristics and treatment responsiveness. Additionally, it was observed that Asian populations seemed to derive a greater benefit compared to Western populations. These differences may be influenced by genetic, environmental, racial, and healthcare-related factors that affect cancer progression and treatment outcomes. The quality of the included studies was also evaluated and found to be of average sufficient quality. However, the presence of publication bias, as indicated by Begg's and Egger's tests, suggests that studies reporting positive outcomes are more likely to be published, potentially biasing the overall results. To address this concern, the Trim and Fill technique was employed to compensate for any missing studies, resulting in a slightly reduced but still significant estimate for the survival advantage. Several mechanisms explain the enhanced survival

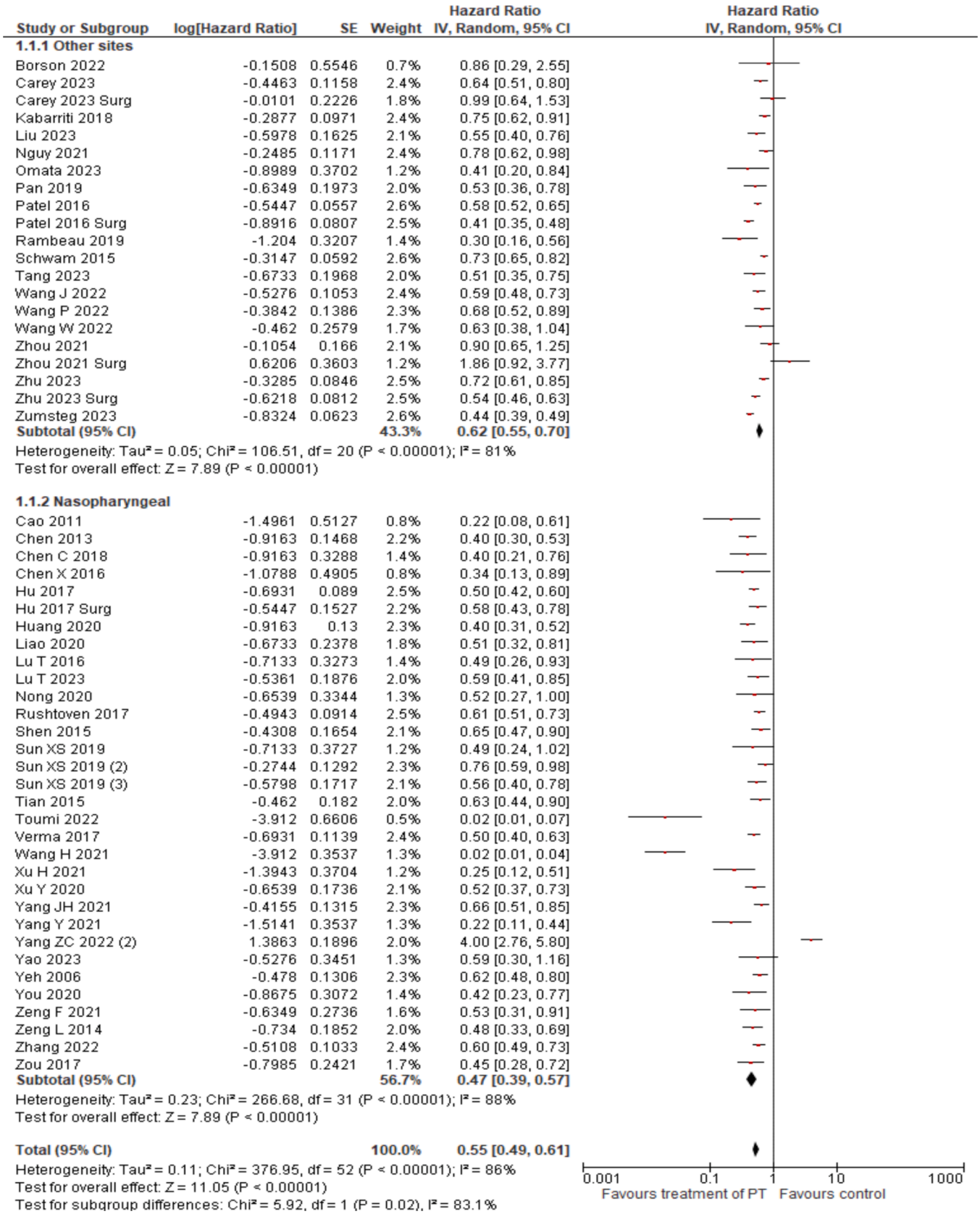

Fig. 2. Overall survival with addition of primary tumor treatment to systemic therapy.

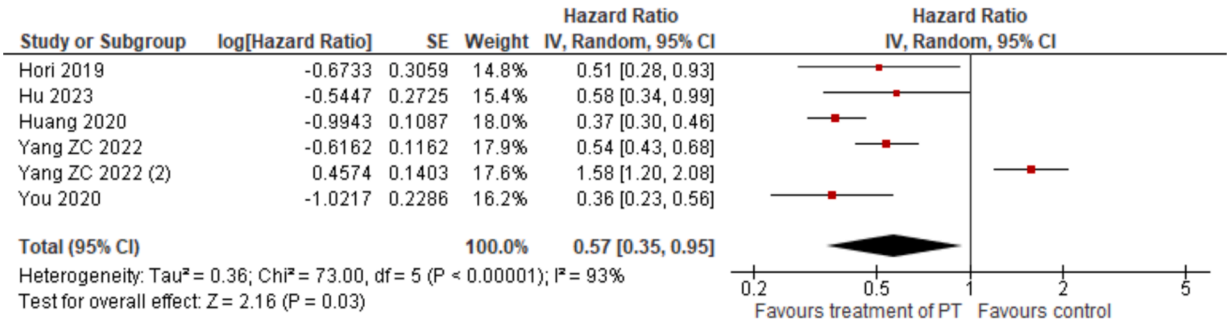

Fig. 3. Progression-free survival with addition of primary tumor treatment to systemic therapy.

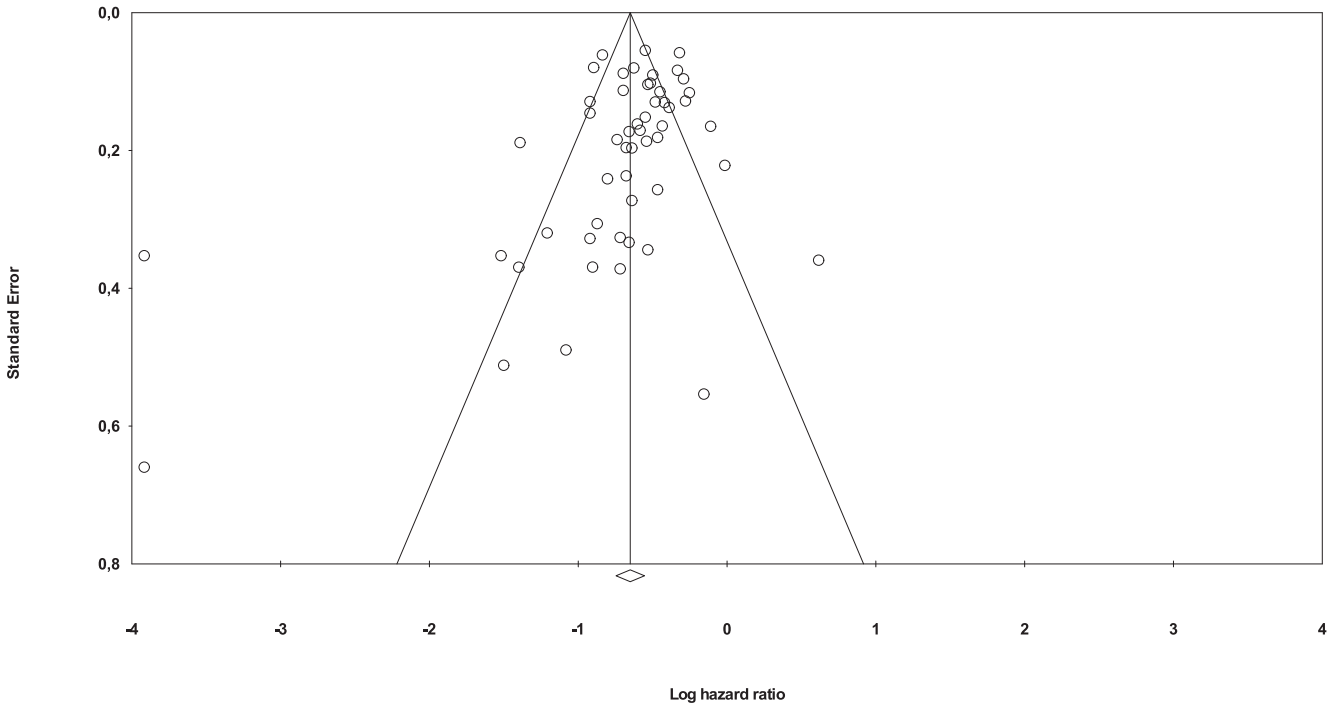

Fig. 4. Funnel plot for publication bias.

outcomes observed with local RT in metastatic nasopharyngeal: 1) local RT, effectively reduces the local tumor mass, potentially decreasing the release of immunosuppressive cytokines and enhancing systemic immune responses; 2) synergy with systemic therapy: combining RT with CT or immune checkpoint inhibitors has been shown to augment antitumor effects by sensitizing tumor cells to systemic agents and promoting an abscopal effect, where localized radiation induces systemic immune responses against metastatic lesions; 3) improved local control: for nasopharyngeal cancer, where the primary tumor frequently causes significant symptoms such as nasal obstruction, cranial nerve palsies, and pain, RT provides symptomatic relief and enhances the quality of life.

Despite the promising findings, this study acknowledges several limitations. The high heterogeneity among the included studies suggests variability in patient populations, treatment protocols, and study designs, which may impact the generalizability of the results. Additionally, the presence of publication bias highlights the likelihood of positive studies being published, which can skew the overall findings. Despite the Trim and Fill method being used to address missing studies, resulting in a slightly lower but still significant estimate for the survival benefit, it has notable limitations, particularly in the context of high heterogeneity. As highlighted by Shi et al., [54] significant variability among included studies may impair the accuracy and power of this method. Given the high heterogeneity ($I^2 = 86$ %) observed in this *meta*-analysis, the Trim and Fill adjustment results should be interpreted cautiously. Furthermore, most of the included studies were retrospective in nature, introducing bias and potential confounding factors. Only one study was a randomized phase III trial, underscoring the need for more high-quality prospective research to validate these findings. Additionally, we were unable to differentiate the effect size between locoregional treatments in the context of de novo metastatic head and neck cancer (which constituted the majority of patients treated) or synchronous metastasis.

Despite these limitations, the outcomes of this *meta*-analysis have important clinical implications as they advocate for a personalized approach to managing metastatic HNC. The decision to treat the primary tumor and neck nodes should be based on individual patient characteristics, tumor biology, and overall health condition. Patients with a favorable performance status and limited metastatic burden are expected to benefit the most from aggressive locoregional treatment and patients who respond well after the initial cycles of systemic therapy. Customizing treatment plans to meet the specific needs of patients requires consideration of factors such as tumor location, extent of metastasis, genetic and molecular profiles, response to systemic therapies, and patient preferences. The involvement of multidisciplinary teams, including oncologists, surgeons, radiologists, and other specialists, is

crucial in developing and implementing these personalized treatment strategies. Future research efforts should prioritize prospective randomized trials to validate these findings and overcome the limitations associated with retrospective studies. Furthermore, investigations into the molecular mechanisms underlying the observed benefits of locoregional therapy should be pursued, as they may pave the way for the development of more precise and effective treatment modalities. Additionally, exploring the impact of novel systemic agents, such as immunotherapies and targeted therapies, in combination with locoregional interventions could significantly improve patient outcomes by modifying the tumor microenvironment and enhancing the overall treatment approach. Emerging strategies, such as personalized radiation therapy, which leverage cutting-edge imaging technologies and biomarkers to tailor treatment for individual patients, show great potential. Stereotactic and adaptive radiation therapy techniques, which adapt treatment protocols based on tumor response and anatomical variations, exemplify the application of precision medicine in radiation therapy. These approaches improve treatment precision and efficacy and minimize adverse effects, thereby enhancing the overall quality of life for patients.

In conclusion, this *meta*-analysis provides compelling evidence supporting the effectiveness of treating the primary tumor and neck nodes in patients with metastatic HNC, resulting in improved survival outcomes. The incorporation of surgery and/or radiation therapy with systemic therapies represents a promising strategy for addressing this complex condition. However, caution is necessary when interpreting the magnitude of these findings due to significant limitations. The lack of stratified data distinguishing between oligometastatic and polymetastatic patients, inadequate reporting on systemic therapy details, and the absence of toxicity and quality-of-life evaluations restrict the applicability of the results. Additionally, the high heterogeneity among studies and publication bias highlight the necessity for well-designed prospective randomized trials to validate these findings and enhance treatment protocols. Careful patient selection is essential to balance the potential benefits against the risks of locoregional treatments.

CRediT authorship contribution statement

Fausto Petrelli: Writing – review & editing, Writing – original draft, Validation, Formal analysis, Conceptualization. **Luigi Lorini:** Validation, Data curation. **Alberto Paderno:** Validation, Data curation. **Daniela Carioli:** Validation. **Francesca Trevisan:** Validation. **Vincenzo Capriotti:** Validation. **Massimiliano Nardone:** Validation. **Cristina Gurizzan:** Validation, Data curation. **Carlo Resteghini:** Validation, Data curation. **Paolo Bossi:** Writing – review & editing, Writing – original draft, Validation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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