

The Economic Burden of Head and Neck Cancer: A Systematic Literature Review

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Published online: 20 May 2014

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Abstract

Background This systematic literature review aimed to evaluate and summarize the existing evidence on resource use and costs associated with the diagnosis and treatment of head and neck cancer (HNC) in adult patients, to better understand the currently available data. The costs associated with HNC are complex, as the disease involves

multiple sites, and treatment may require a multidisciplinary medical team and different treatment modalities.

Methods Databases (MEDLINE and Embase) were searched to identify studies published in English between October 2003 and October 2013 analyzing the economics of HNC in adult patients. Additional relevant publications were identified through manual searches of abstracts from recent conference proceedings.

Results Of 606 studies initially identified, 77 met the inclusion criteria and were evaluated in the assessment. Most included studies were conducted in the USA. The vast majority of studies assessed direct costs of HNC, such as those associated with diagnosis and screening, radiotherapy, chemotherapy, surgery, side effects of treatment, and follow-up care. The costs of treatment far exceeded those for other aspects of care. There was considerable heterogeneity in the reporting of economic outcomes in the included studies; truly comparable cost data were sparse in the literature. Based on these limited data, in the US costs associated with systemic therapy were greater than costs for surgery or radiotherapy. However, this trend was not seen in Europe, where surgery incurred a higher cost than radiotherapy with or without chemotherapy.

Conclusions Most studies investigating the direct healthcare costs of HNC have utilized US databases of claims to public and private payers. Data from these studies suggested that costs generally are higher for HNC patients with recurrent and/or metastatic disease, for patients undergoing surgery, and for those patients insured by private payers. Further work is needed, particularly in Europe and other regions outside the USA; prospective studies assessing the cost associated with HNC would allow for more systematic comparison of costs, and would provide valuable economic information to payers, providers, and patients

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Key Points for Decision Makers

Head and neck cancer (HNC) is the sixth most common malignancy globally, and poses a substantial economic burden to payers, healthcare systems, and patients. Costs associated with HNC are driven by complex treatment pathways and the need for involvement of several medical specialties.

Studies published from 2003 to 2013 mainly examined direct costs of HNC, using data for the USA. Few reports were available in the literature describing indirect costs of the disease. Direct costs of treatment appeared to be the main driver of costs of HNC. In comparison, costs associated with diagnosis, treatment-related side effects, or follow-up care were minimal.

Considerable variation among studies regarding the specific type of HNC within the patient population, data sources, costing years, and healthcare systems made meaningful comparisons challenging given the available evidence. Prospective studies, such as patient registries or trials with economic endpoints, are needed to facilitate a systematic evaluation of the economic burden of HNC and comparative value of alternative treatment modalities.

1 Introduction

1.1 Definition

Head and neck cancer (HNC) encompasses neoplasms found in the oral cavity, pharynx, larynx, sinuses, and salivary gland, and is common throughout the world. The collective group of HNC, though heterogeneous in location, most often arises in the squamous cells of epithelial surfaces, and is often referred to as squamous cell carcinoma (SCC) of the head and neck (SCCHN).

1.2 Epidemiology

Head and neck cancer is the sixth most common cancer worldwide [1], and in 2013, 2.5 % of new cancer diagnoses in the USA were estimated to be HNC [2]. Based on recently released data for Europe from the World Health Organization, the age-standardized incidence rate for HNC varies from 3.5 per 100,000 in Cyprus to 23.0 per 100,000 in Hungary. Within the five most populous European countries [EU5: UK, Italy, Germany, France, and Spain], the range is much smaller, from 7.7 per 100,000 in Italy to

13.9 per 100,000 in France [3]. HNC incidence has remained relatively stable over the past 10 years, and risk factors for its occurrence have been fairly well established. Notably, tobacco and alcohol use are associated with higher HNC risk. The role of infection with human papillomavirus (HPV) is less clear, although such infection appears to be more commonly associated with oropharyngeal cancer, and possibly associated with better prognosis compared with other factors [4, 5].

1.3 Management

While HNC incidence has remained stable, treatment and patient management have become more complex, often requiring a multidisciplinary team of oncologists, surgeons, radiation therapists, nutritionists, pharmacists, and speech therapists. In North American and European clinical practice, patients with early stage HNC (approximately one-third of those presenting with HNC) typically tend to receive a single main treatment modality: radiotherapy or surgery [6, 7]. The majority of patients (approximately 50 %), who are diagnosed with locally advanced HNC, are typically treated with a combination of treatment modalities including concurrent radiotherapy and chemotherapy [concurrent chemoradiation therapy (CRT)], with surgery if indicated [6]. The remaining patients (about one-fifth), who present with metastatic disease, are usually treated with palliative chemotherapy [6].

Depending on HNC severity and progression, the goal of HNC therapy is either cure or palliation. However, a significant amount of rehabilitation and supportive therapies are also required for and concomitantly administered to HNC patients to maintain or restore patients' normal function and activities. Reconstructive surgery and prostheses are important means of rehabilitation. Multidisciplinary rehabilitation also can take the form of nutritional support, dietary counseling, and speech therapy. Additionally, follow-up care and surveillance are important, as significant morbidity and mortality in this patient group are associated with recurrent disease, rather than metastatic disease as is more common in other oncologic indications [6]. These multifaceted treatment approaches (of primary and supportive regimens) have improved health-related quality of life, morbidity, and mortality [8].

1.4 Research Objective

The past decade has seen substantial changes in the treatment of HNC, with approval of new agents for systemic therapy, and more widespread application of advancements such as robotic surgery and intensity-modulated radiotherapy (IMRT). While these measures frequently reduce treatment-related toxicity and morbidity, they also may

contribute to additional costs of treatment. This review sought to examine the reported healthcare costs and resource use associated with diagnosis, treatment, and follow-up care for HNC. Admittedly, such a review is made difficult by (1) the heterogeneity of HNC sites; (2) the multidisciplinary nature of the healthcare provider team and the heterogeneity of treatment that they administer; as well as (3) practice pattern differences across geographic regions. However, with these issues recognized, the research was undertaken to gain a better understanding of the economics associated with current medical practice in HNC. This information can inform the multiple stakeholders—patients, providers, payers, and health technology assessment authorities—who are interested in the economic burden of HNC and the positive or negative impacts on that burden associated with current and future healthcare technologies and services. As such, this review can serve as the new baseline for future comparative research.

2 Methods

A search of the medical literature was conducted in MEDLINE (via PubMed) and Embase to identify relevant English-language publications describing the economic burden of HNC. The search identified publications using specific keywords related to “head and neck, oropharyngeal or laryngeal” and other HNC sites and “cancer”, and those related to relevant economic outcomes, including “cost, resource utilization, economic or work loss”. Keywords had to be located in the title or abstract of full-length publications, and studies had to be conducted in humans and published within the 10 years preceding the search (i.e., October 2003 to October 2013). Articles were included if they reported on overall costs or resource utilization relating to screening and diagnostic procedures, interventions and treatments, side effects/symptoms of treatment (i.e., complications from surgery), or follow-up care in an adult population of patients with HNC. Articles were excluded if they did not report on economic outcomes for HNC or for an adult population. Articles were also excluded if the costs described were not directly derived from research original to the published work. Narrative (non-systematic) reviews; genetic, cellular, or molecular studies; case reports; case series; and conference abstracts published prior to 2012 were also excluded.

The MEDLINE and Embase searches yielded 833 abstracts (323 from MEDLINE and 510 from Embase), with some overlap between the two databases. After removing the duplicate articles indexed on both MEDLINE and Embase, there were 606 unique publications. The abstracts identified by the search were manually reviewed by a single researcher, with those abstracts that did not

meet any exclusion criteria examined as full-text publications. A total of 169 abstracts were selected for full-text review. The full-text articles were assessed by two independent investigators for eligibility for inclusion using the same inclusion and exclusion criteria applied during abstract screening. Any disagreements between the two reviewers were resolved by a third independent reviewer. Conference proceedings [American Head and Neck Society (AHNS), American Society for Clinical Oncology (ASCO), European Head and Neck Society (EHNS), European Society for Medical Oncology (ESMO), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR)] from the past 2 years (i.e., 2012 and 2013) were also examined to identify relevant abstracts for inclusion.

Articles were included in the final review if they did not meet any of the exclusion criteria during full-text review. Seventy-five articles, including nine abstracts selected from conference proceedings, describing the economic burden of HNC were identified for inclusion in the systematic literature review [9–82]. The 103 full-text articles that were excluded were ineligible for the review because of their publication date ($n = 23$), study design ($n = 6$), patient population ($n = 14$), or outcomes reported ($n = 60$). A single researcher evaluated the level of evidence for each study using criteria from the University of Oxford’s Centre for Evidence-Based Medicine (CEBM) Levels of Evidence 1 guidelines (2009) [83, 84]. CEBM ratings were only given to peer-reviewed literature published in MEDLINE and Embase. Overall, the quality of the identified literature was relatively poor; all studies received a CEBM rating of either 3b or 4. A summary of the full systematic literature search strategy is presented in Fig. 1.

3 Results

3.1 Societal Costs of Head and Neck Cancer (HNC)

The full societal burden of HNC consists of the substantial direct medical expenditures associated with the disease, but also incorporates indirect costs, such as reduced workforce participation and premature mortality, and the resultant loss of productivity. To accurately analyze the societal cost of this disease, economic evaluations of HNC must incorporate both direct and indirect costs. In the current review, no such studies met the inclusion criteria; however, a few recent publications provided context for the societal burden of HNC.

In the USA and France, direct and indirect costs contributed similarly to the overall societal cost of HNC, with direct costs slightly higher than indirect costs in both countries. National US expenditures in 2010 were

calculated by combining 2010 cancer prevalence by cancer site and phase of care with annualized expenditures associated with cancer care in 2010 dollars. This estimate of direct medical costs for HNC totaled US\$3.64 billion in 2010 [85]. Similarly, a study assessing earnings lost as a measure of productivity found that in 2010, the value of lost productivity due to HNC was US\$3.4 billion. Based on projected growth and aging of the US population, productivity costs will increase if cancer mortality rates are constant in the future [86]. In addition, a French study examining the “social” burden of laryngeal cancer attributable to occupational exposure to asbestos reported that direct costs for this condition ranged from €35.3 million to 57.6 million, while indirect costs were €17.5 million to 34.9 million (2010 €) [87].

3.2 Total Direct Medical Costs of HNC

The direct medical costs of HNC have been assessed in 12 studies. Most (nine of 12) have used commercial or publicly available US databases of administrative claims [9, 20, 34, 38, 41, 50, 54, 55, 78], with one each using the Hospital Episode Statistic (HES) database in the UK [37], hospital records from five Dutch university hospitals [69], or a regional cancer center in Brazil [51]. Time horizons,

databases, demographic and disease subpopulations, and costing years have ranged widely, hindering comparisons. However, each economic snapshot taken from a different angle shows that HNC presents high direct costs to payers.

3.3 Per-Patient Direct Medical Costs

3.3.1 Excess Cost Approach

In the US, most efforts to calculate the per-patient direct medical costs of HNC have taken an excess cost approach, with the difference between HNC patients and controls without HNC representing the cost of the disease. Studies reporting per-patient direct medical costs are summarized in Table 1. Broadly comparable data are highlighted in this table; for the sake of brevity and ease of use, not all available data are presented in the tables.

Five-year excess costs were calculated by two studies using Medicare claims linked to data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute from different time periods: patients newly diagnosed with SCCHN in a SEER registry between 1991 and 1993 [41], and those whose first diagnosis of a primary tumor of the head and neck occurred between 1995 and 2005 [78]. Using a costing year of 1998 US dollars (US\$), patients in the earlier study incurred an average of US\$25,542 more than matched controls, with mean Medicare costs of US\$48,847 per patient (US\$53,741 for those with distant metastases, US\$58,387 with regional spread, US\$42,698 with local disease, US\$37,434 with in situ disease) [41]. In the later study, which used a costing year of 2010 US\$ and excluded prescription drugs, patients incurred 5-year costs of US\$34,489 more than matched controls, with mean costs to Medicare of US\$79,165 per patient [78]. All patients in both studies were elderly, as Medicare is the program that insures Americans over the age of 65 years. While for some conditions this might limit generalizability, HNC is diagnosed in the USA at a mean age of 62 [88, 89], and thus a large percentage of the disease population would be expected to be insured by Medicare.

Two other recent studies using excess cost approaches with data sources that included some patients insured by Medicare examined different patient subgroups, limiting comparisons. Both analyzed data from a commercial database and the Medicare database, with one adding data from other sources, including Medicaid, the program designed to insure the poor and disabled. Kim Le et al. [38], using commercial and Medicare data, calculated a 6-month adjusted cost to public and private US payers of US\$60,414 for metastatic and US\$21,141 for recurrent disease (2008 US\$). Most of the incremental cost stemmed from outpatient visits, approximately a third from inpatient

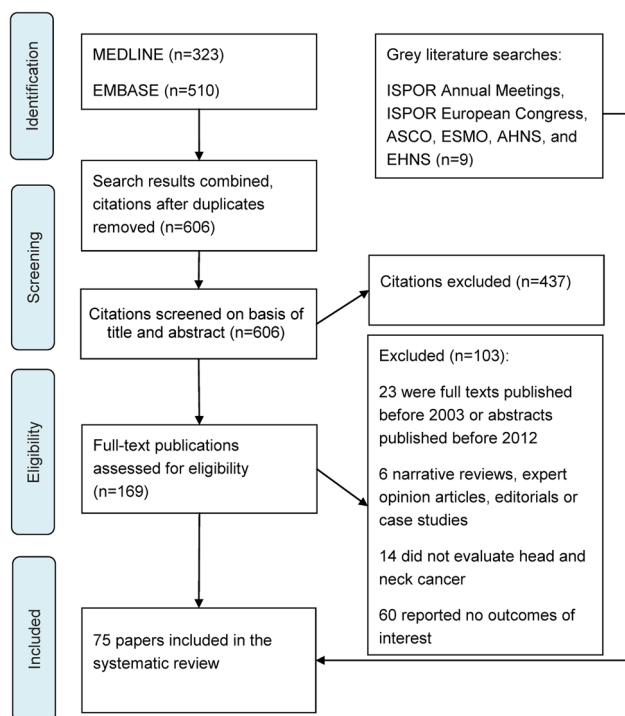


Fig. 1 Systematic search and screening flow chart. *AHNS* American Head and Neck Society, *ASCO* American Society for Clinical Oncology, *EHNS* European Head and Neck Society, *ESMO* European Society for Medical Oncology, *ISPOR* International Society for Pharmacoeconomics and Outcomes Research

Table 1 Per-patient burden of illness of head and neck cancer

References	Country	Parameter	Year of reported costs	Reported cost
Excess cost approach				
USA				
Hollenbeak et al. [78]	USA	Total 5-years costs	2010	US\$79,165
		Total 5-year costs for controls		US\$44,676
Jacobson et al. [34]	USA	Annual healthcare costs for commercially insured patients	2009	US\$71,151
		Annual healthcare costs for Medicare patients		US\$35,890
		Annual healthcare costs for Medicaid patients		US\$44,541
Kim Le et al. [38]	USA	Total costs for metastatic cancer over 6 months	2008	US\$65,412
		Total costs for metastatic cancer controls over 6 months		US\$3,168
		Total costs for recurrent locally advanced cancer over 6 months		US\$25,837
		Total costs for recurrent locally advanced cancer controls over 6 months		US\$2,752
Lang et al. [41]	USA	Mean Medicare payments	1998	US\$48,847
		Mean Medicare payments for controls		US\$23,305
		Mean Medicare payments for distant cancer		US\$53,741
		Mean Medicare payments for regional cancer		US\$58,387
		Mean Medicare payments for local cancer		US\$42,698
		Mean Medicare payments for in situ cancer		US\$37,434
Ray et al. [54]	USA	Mean monthly total healthcare costs for patients with dermatologic side effect	2010	US\$12,539
		Mean monthly total healthcare costs for patients without dermatologic side effect		US\$9,684
Reveles et al. [55]	USA	Median total direct cost pre-cetuximab approval	NR	US\$110,099
		Median total direct cost post-cetuximab approval		US\$111,156
Attributable cost approach				
Europe				
Kim et al. [37]	UK	Mean annual postoperative healthcare utilization	2008–2009	£23,212
USA				
Amonkar et al. [9]	USA	Mean annual healthcare costs	2008	US\$34,450
Coughlan and Frick [20]	USA	Mean cost per case (condition approach)	2008	US\$14,573
		Mean cost per case (attributable approach)		US\$4,788
Rest of world				
Pinto and Uga [51]	Brazil	Mean total cost of treatment for laryngeal cancer over 6 years	2006	R\$37,529
		Mean total cost of treatment for laryngeal cancer for the first year of treatment		R\$27,667

£ Great Britain pounds, NR not reported, R\$ Brazilian reais, US\$ US dollars

costs, and 11–13 % from drug cost. Patients with both metastatic and recurrent disease had high use of supportive care [38]. Jacobson et al. [34] reported 1-year costs of US\$71,151 for commercially insured patients, US\$35,890 for those insured by Medicare, and US\$44,541 for those insured by Medicaid (2009 US\$).

Three other studies in the USA used commercial databases to examine cost of illness in specific subgroups defined by adverse reaction to drug treatment. Pike et al. [50] looked at a small sample ($n = 27$) of patients who had chemotherapy-associated peripheral neuropathy, calculating that those with HNC incurred US\$36,660 more

annually to a commercial payer than matched controls without peripheral neuropathy (2006 US\$). Outpatient treatment accounted for the largest part of these costs. Reveles et al. [55] compared cohorts of patients before and after approval of cetuximab in the USA in 2006 (although it was approved specifically for HNC in 2011 [90]), finding no significant differences in total costs to a commercial payer (US\$110,099 pre-cetuximab, US\$111,156 post-cetuximab) [costing year not reported (NR)]. Treatment costs constituted nearly 90 % of these median totals, chiefly because of outpatient costs and radiation [55]. The cost to a payer of dermatologic reactions to cetuximab was assessed

by Ray et al. [54], who reported that among 971 HNC patients given cetuximab, the 333 who had an adverse reaction had average monthly healthcare costs of US\$12,539, compared with US\$9,684 for patients with no adverse reaction (2010 US\$). The difference largely resulted from additional hospitalization costs among patients with reactions.

3.3.2 Attributable Cost Approach

Attributable costs, those that are directly coded to HNC, have been assessed in a variety of databases. These studies encompass two in the USA [9, 20] and one each in the UK [37], Brazil [51], and the Netherlands [69]. In the USA, annual attributable costs to a payer may range from US\$5–35,000, depending on the way the population is defined. The high end of this range was estimated by Amonkar et al. [9], who identified 1,104 commercially insured patients in a claims database who were undergoing surgical resection for HNC in the mid-2000s. These patients were estimated to incur a mean total healthcare cost per patient of US\$34,450 annually (2008 US\$). Another analysis of US costs of HNC in commercial or Medicare data found far lower costs, possibly because patients identified by the earlier study were undergoing surgery and incurring inpatient costs. This second analysis, which used data from the Medical Expenditure Panel Survey (MEPS), calculated attributable costs of HNC of US\$4,788 per case per year, largely to private payers. In contrast with the previous study, outpatient visits tended to drive these (correspondingly lower) costs [20]. However, only 120 patients with this cancer could be identified in the MEPS, and only 103 with events attributable to HNC, underscoring the authors' recommendations to use the results of the different costing approaches as a range (thus approximately US\$5–15,000 per patient per year) rather than precise point estimates [20].

The authors of this MEPS study also took a “condition approach” to calculating direct medical costs, pooling consolidated year files and condition files to estimate healthcare utilization and expenditures in patients with this cancer. This “condition approach” yielded a higher annual cost of US\$14,573 per case, with most costs associated with inpatient care and notably higher than the results of the attributable cost approach in which costs stemmed from outpatient care. Outside the USA, data from five university hospitals in the Netherlands were examined for patients with laryngeal cancer; total mean costs per patient from diagnosis through 1-year follow-up ranged from €8,232 to €24,290, with increasing cost associated with more advanced disease [69]. A Brazilian analysis of the costs of laryngeal cancer in patients with a history of smoking found that the mean total cost per patient over a 6-year

follow-up post-diagnosis was 37,529 Brazilian reais (R\$). The mean cost for the first year of treatment alone was R\$27,667 (2006 R\$); the main drivers of cost were radiotherapy and hospitalization [51]. Similarly, in the UK, Kim et al. [37] used the HES database linked to mortality records, and found that during the 5 years following resection, HNC patients cost the National Health Service (NHS) 23,212 Great Britain pounds (£) (2008–2009 £) per patient. Nearly all of this cost (£19,778) was incurred during the first year after resection, serving as a reminder of why it is not possible to multiply annual costs of illness by five to compare them to 5-year totals.

3.4 Overall Direct Medical Costs

Overall direct medical costs of HNC were estimated by three studies: one in the UK using the HES database linked to mortality data [37], one in the US using linked SEER–Medicare data [78], and another US study using the MEPS database [20]. In the UK, Kim et al. [37] examined data from 11,403 patients after resection for HNC and estimated that the cost to the NHS totaled £255.5 million over a possible 5-year follow-up (2008–2009 £). The study by Hollenbeak et al. [78] of linked SEER–Medicare data of an elderly HNC cohort ($n = 10,711$) reported that, over 5 years, excess costs to Medicare of HNC care would total US\$369 million (2010 US\$) compared with a matched cohort of patients without HNC. Using the MEPS database, Coughlan and Frick [20] took both an attributable and a condition costing approach (described above) to generate a range of estimates. With the condition approach, national yearly expenditures in the USA totaled US\$16.47 billion (2008 US\$). Attributable costs yielded annual expenditures for all HNC-associated events of US\$8.49 billion, although, as noted above, only 120 respondents to the MEPS survey had HNC, and only 103 had events attributable to the cancer.

3.5 Cost Analyses: Diagnostic Methods

Despite the technology and medical strategies involved in diagnosis, the cost of this phase of care is eclipsed by that of the treatment phase. In the US database study described above, Reveles et al. [55] used commercial insurance claims to compare the costs of each component of care, finding that prior to the approval of cetuximab in the USA in 2006 (it was specifically approved for HNC in 2011), the diagnosis phase cost US\$5,053 per patient, significantly less than after cetuximab's approval (US\$6,860, costing year NR). Cetuximab would be expected to raise the cost of the diagnosis phase in another cancer indication, metastatic colorectal cancer, as patients with this cancer receive companion diagnostic testing (for K-ras mutation) for

eligibility to take the drug. However, companion diagnostic testing is not required for use of cetuximab in HNC. Therefore, a post-cetuximab rise in diagnostic costs in HNC could simply result from a rise in diagnosis costs over time rather than a specific effect of cetuximab [90].

In the current review, six studies analyzed the costs of diagnostic approaches to HNC. In Canada, Australia, and the Netherlands, three studies suggested that combined positron emission tomography (PET)/computed tomography (CT) approaches yielded economic benefits when used to assess metastatic spread and nodal response [40, 53, 68]. Two studies examined the use of telemedicine to facilitate meetings with specialist physicians, finding that this approach saved costs in Sweden and Scotland [24, 64]. A Dutch study assessed the cost of including a chest CT scan in the initial tumor staging of patients with oral SCC [35].

3.5.1 Imaging

Positron emission tomography/computed tomography imaging, a diagnostic modality that has improved diagnostic accuracy and thus grown in importance over the last decade [91, 92], was found to provide economic benefits in three studies, and to present an acceptable cost-benefit screening option in a fourth study [35, 40, 53, 68].

In a chart review in Canada and a cost-minimization analysis in Australia, the cost of PET/CT to the health service was offset by reducing additional procedures or treatments. Using charts of 76 patients with advanced disease in Alberta, Canada, Kurien et al. [40] calculated that diagnostic workup using PET/CT cost 722 Canadian dollars (C\$), versus only C\$450 for a workup without it (costing year 2008–2009 C\$ for examinations, 2005–2006 C\$ for treatment). However, the patients whose cancer would only have been identified as metastatic using PET/CT could be treated with palliation, reducing the cost of treatment in this group by nearly C\$200,000 and sparing the patients unnecessary treatments. The Australian cost-minimization analysis of a prospective study found that assessing nodal response with modalities incorporating PET avoided the need for many neck dissections. The strategy of using PET only for patients found (initially by CT) to have an incomplete response incurred the lowest costs to the Australian health service [2,111 Australian dollars (A\$) vs. A\$16,502 for planned neck dissection and A\$8,014 for CT alone (2008–2009 A\$)] [53].

Two Dutch studies also found economic benefits of PET/CT. A prospective study of 80 patients at high risk for distant metastases found that CT plus ¹⁸F-fluorodeoxyglucose (FDG) PET was a dominant strategy for pre-treatment screening over either imaging modality alone, meaning that it was both more effective (sensitive) and

saved costs (€203–604, costing year NR) [68]. Another analysis of patients with oral SCC found that including a chest CT in the initial screening workup cost €8,214 (costing year NR) for each patient benefitting from the chest CT scan (each pulmonary malignancy identified). This cost was considered by the authors to align with screening and diagnosis costs in the Netherlands for several other types of cancer, such as breast (€8,134) and cervical cancer (€10,270) [35].

3.5.2 Telemedicine

Costs of diagnosis include not just tools of diagnosis but also the need to bring together patients and specialists, and two studies found that telemedicine saved costs over meeting in person [24, 64]. A survey study of 84 HNC patients in Sweden found that while face-to-face meetings for either diagnosis or treatment cost 2,267 Swedish kronor (SEK), meetings conducted by telemedicine cost SEK2,036. The responsible physician tended to participate in telemedicine meetings but not in-person meetings, which raised the cost but also the value of the telemedicine. It should also be noted that telemedicine costs may be lower now than when the study was conducted, with costs of this study expressed in 1999 SEK. Videoconferencing in Scotland also saved costs over meeting in person, with 42 patients assessed for HNC using telemedicine (£77/patient) or face to face (£383) (costing year NR) [24, 64].

3.6 Cost Analyses: Treatment Approaches

As studies of direct medical costs for HNC have found, treatment comprises a large percentage of the overall costs of care for patients with this cancer. Reveles et al. [55], analyzing commercial US insurance claims, calculated that treatment costs represented 89.3 % of the total cost of care for SCC/HN. In the current review, 21 studies identified costs related to specific treatment approaches: ten from the USA [21, 27–31, 33, 43, 44, 56, 61, 81, 82], three from Canada [14, 23, 62], two from France [12, 77], and one each from India [67, 93], Thailand [71], Greece [26], Spain [58], the UK [66], and a multicenter study in Europe [79]. A variety of study designs were used, including database studies (principally in the US), chart reviews, and randomized trials. Studies describing direct costs for the various HNC treatment modalities are summarized in Table 2.

3.6.1 Hospitalization

Studies assessing the costs of hospitalization in HNC have been conducted in Thailand [71], Spain [22], France [63], the UK [66], and the USA [33, 43, 56]. While it is not possible to compare these costs across different countries

Table 2 Cost-comparison and cost-identification analyses within treatment approaches for head and neck cancer

Reference	Country	Parameter	Year of reported costs	Reported cost
Surgery				
Europe				
Bodard et al. [12]	France	Cost of extraoral repositioning system used during surgery	NR	€50
		Cost of intraoral repositioning system used during surgery		€30
Hammoudi et al. [77]	France	Cost savings of transoral robotic surgery (vs. conventional surgery) per case treated	NR	\$7,134 ^a
O'Connor et al. [79]	Europe	Cost of a positive SLNB pathway result per patient	NR	€17,186–18,244
		Cost of a negative SLNB pathway result per patient		€4,715
		Cost of a false negative SLNB pathway result per patient		€17,834–19,014
		Cost of traditional surgical approach for stage II oral tumor per patient		€27,515
		Cost of traditional surgical approach for stage I oral tumor per patient		€15,043–15,378
USA				
Gourin et al. [27]	USA	Mean hospital cost of partial laryngectomy	2009	US\$23,623
		Mean hospital cost of total laryngectomy/laryngopharyngectomy		US\$50,980
		Mean hospital cost of pedicled or free flap reconstruction		US\$17,083
Gourin et al. [28]	USA	Mean hospital cost of partial glossectomy	2009	US\$17,410
		Mean hospital cost of total glossectomy		US\$25,990
		Mean hospital cost of pharyngectomy		US\$19,715
		Mean hospital cost of mandibulectomy		US\$19,593
		Mean hospital cost of neck dissection		US\$19,528
		Mean hospital cost of pedicled or free flap reconstruction		US\$17,641
		Mean hospital cost of partial laryngectomy		2011
Gourin and Frick [30]	USA	Mean hospital cost of total laryngectomy/laryngopharyngectomy	2011	US\$37,908
		Mean hospital cost of neck dissection		US\$28,715
		Mean hospital cost of pedicled or free flap reconstruction		US\$30,038
Gourin and Frick [29]	USA	Mean hospital cost of partial glossectomy	2011	US\$24,041
		Mean hospital cost of total glossectomy		US\$25,935
		Mean hospital cost of laryngectomy		US\$26,615
		Mean hospital cost of tonsillectomy		US\$13,763
		Mean hospital cost of pharyngectomy		US\$20,824
		Mean hospital cost of mandibulectomy		US\$19,673
		Mean hospital cost of neck dissection		US\$23,341
		Mean hospital cost of pedicled or free flap reconstruction		US\$22,679
		Mean hospital cost of partial glossectomy		2012
Li et al. [43]	USA	Mean hospital cost of total glossectomy	2012	US\$34,459
		Mean hospital cost of mandibulectomy		US\$32,167
		Mean hospital cost of neck dissection		US\$30,710
		Mean hospital cost of pedicled or free flap reconstruction		US\$31,021
Maddox and Davies [44]	USA	Mean hospital charge for laryngectomy in 1997	2008	US\$58,000
		Mean hospital charge for laryngectomy in 2008		US\$109,000
Richmon et al. [56]	USA	Mean hospital cost of pedicled or free flap reconstruction	2012	US\$33,798
		Mean hospital cost of transoral robotic surgery		US\$16,262
Rest of world				
Brookes et al. [14]	Canada	Cost savings of resection with tracheostomy site sutured (vs. not sutured) per patient	NR	C\$11,609
Smeele et al. [62]	Canada	Mean total cost of pectoralis major myocutaneous flap reconstruction	NR	C\$20,400
		Mean total cost of free flap reconstruction		C\$23,600

Table 2 continued

Reference	Country	Parameter	Year of reported costs	Reported cost
Radiotherapy				
USA				
Razfar et al. [82]	USA	Cost of IMRT for oral pharyngeal cancer per patient	NR	US\$165,537
		Cost of traditional XRT for oral pharyngeal cancer per patient		US\$87,922
		Cost of IMRT for early stage cancer per patient		US\$97,563
		Cost of traditional XRT for early stage cancer per patient		US\$63,374
		Cost of surgery for early stage cancer per patient		US\$61,265
		Cost of IMRT for advanced stage cancer per patient		US\$52,034
Sheets et al. [61]	USA	Cost of traditional XRT for advanced stage cancer per patient		US\$78,046
		Total cost of IMRT (vs. CRT) per patient	NR	US\$5,881
		Pretreatment cost of IMRT (vs. CRT) per patient		−US\$1,700
		Cost during treatment of IMRT (vs. CRT) per patient		US\$4,768
		Follow-up cost of IMRT (vs. CRT) per patient		US\$2,288
Rest of world				
Donato et al. [23]	Canada	Costs for immobilization devices used during radiation therapy for the Uvex system	2004	C\$141
		Costs for immobilization devices used during radiation therapy for the Ultrplast system		C\$82.10
Chemotherapy				
Europe				
Fountzilias et al. [26]	Greece	Cost of PGEM chemotherapy per patient	2005	€7,419
		Cost of PPLD chemotherapy per patient		€11,068
Greskovich et al. [31]	Greece	Cost of inpatient administration (vs. outpatient) of cisplatin per patient	NR	US\$18,664
USA				
Crandley et al. [21]	USA	Cost of TPF induction added to platinum chemoradiation per patient	NR	US\$189,321
		Cost of platinum chemoradiation without TPF induction per patient		US\$150,270

C\$ Canadian dollars, CRT chemoradiotherapy, IMRT intensity-modulated radiotherapy, NR not reported, PGEM pegylated gemcitabine, PPLD pegylated liposomal doxorubicin, SLNB sentinel lymph node biopsy, TPF docetaxel/cisplatin/5-fluorouracil, US\$ US dollars, XRT external beam radiotherapy

^a Abstract reports costs in dollars but does not specify type of dollar

and healthcare systems, each study concluded that the burden of hospitalization costs is high.

The three US studies used the Nationwide Inpatient Sample database and estimated costs per hospitalization of approximately US\$20–23,000 in 2012 dollars. Hennessey et al. [33] identified 48,263 patients with surgical hospitalizations for HNC recorded in this database and estimated a mean cost to hospitals of US\$22,927 for each hospitalization (2012 US\$). Major surgical procedures were the factor most associated with increased costs (US\$15,682 increase), followed by multiple comorbidities (US\$8,869 increase for three or more) and treatment at a teaching hospital (US\$6,361 increase). Similar costs were calculated by other studies of patients hospitalized with oral malignancy (US\$20,934; 2012 US\$) [43], and oropharyngeal neoplasm (US\$20,547; 2012 US\$) [56]. In each of these analyses, costs were derived by applying a cost-to-charge

ratio to hospital charges, which are problematic because the hospital may be reimbursed amounts that differ greatly from the amounts the hospital charged for its services [44].

Hospitalizations for forms of HNC also presented large costs to national health systems in Europe and Thailand. In the UK, an analysis using the HES database estimated that payments to NHS hospitals in England for HNC hospitalizations total approximately £57.1 million annually (costing year NR). Hospitalizations for oral cavity cancers totaled £12.5 million for men and £7.6 million for women; for oropharyngeal cancers, costs were £13.3 million for men and £4.3 million for women; and for laryngeal cancers, costs were £16.2 million for men and £3.2 million for women [66]. A study using the French national hospital database reported that, in 2007, hospitalizations for HNC cost €323 million, or €2,764–7,673 per patient. Interestingly, the authors attributed €138 million of this cost to the

26 % of HNC caused by HPV infections [63]. A retrospective study of patients treated for glottic cancer in Spain found that mean hospital costs per day were €600–700 (costing year NR) [22]. While the vast majority of database studies are done in Western countries, a study using national health data in Thailand reported that, in 2010, hospital charges totaled 691 million Thai baht (THB) (at the time, US\$21.8 million), or THB26,556 (US\$838) for each of the 26,012 admissions for diagnosis and treatment of HNC [71].

3.6.2 Surgery

A set of 14 studies widely variable in design, geography, procedure assessed, and type of disease evaluated costs of surgery for HNC. Nine studies in the USA, two in Canada, two in France, two in Spain, and one across Europe assessed costs of different surgical approaches for HNC [12, 14, 22, 27–30, 43, 44, 56, 58, 62, 77, 79].

Transoral approaches were judged to be less expensive than traditional approaches in studies conducted in Spain, France, and the USA. In Spain, transoral carbon dioxide laser cordectomy was found to be much less costly (€2,290) than laryngofissure cordectomy (€13,230) (costing year NR) [22] in treating patients with glottic cancer. A retrospective study of 21 patients with an SCC of the upper aero-digestive tract treated at a French hospital found that transoral robotic surgery (TORS) was significantly less expensive than conventional surgery, requiring fewer tracheotomies, shortening stays, and saving \$7,134 (specific currency not reported) [77]. Similarly, a US study of 9,601 patients with oropharyngeal neoplasms reported that use of TORS resulted in mean per patient savings of US\$4,285 (2012 US\$) [56].

Other surgical innovations designed as less invasive may or may not save costs. Maddox and Davies [44], using a database that samples US hospital discharges, determined that mean hospital charges for laryngectomies grew from approximately US\$58,000 in 1997 to US\$109,000 in 2008 (2008 US\$). However, the rise in charges was accompanied by a rise in larynx-sparing approaches, with the number of laryngectomies falling by nearly half over the same period [44]. O'Connor et al. [79], using data from three centers participating in the European Sentinel Node Trial (SENT) for early oral SCC, estimated that the sentinel lymph node biopsy pathway costs approximately 34–56 % of a traditional surgical pathway. The authors calculated that the latter treatment costs €15,043–15,378 for a stage I tumor, and €27,515 for a stage II tumor (costing year NR). In both a Canadian and a Spanish study, minimal cost difference was reported between two types of surgical reconstruction. In the Spanish study of 60 patients undergoing oral cavity

reconstruction following tumor resection, total costs within the first year of treatment were similar for microvascular tissue transfer and for use of local or regional flaps; both costs were approximately €50,000 (costing year NR) [58]. Similarly, the Canadian study of patients with oral or oropharyngeal cancer found that free flap (C\$23,600) and pedicled flap (C\$20,400) surgery had comparable costs [62]. These costs are likely to vary by the location of the cancer; three US studies using the National Inpatient Sample database found that costs for pedicled or free flap reconstruction ranged from US\$10,087 (2012 US\$) for patients with an oral malignancy to US\$22,679 (2011 US\$) for HNC patients with any oropharyngeal cancer [29, 43, 56].

3.6.3 Radiotherapy

The costs of radiotherapy have been evaluated in three studies; a chart review and a database study from the US reported greater costs of IMRT compared with conventional radiotherapy [61, 82], and a trial from Canada [23] assessed the costs of immobilization systems used during this form of treatment.

Several different radiotherapy approaches are utilized in the treatment of HNC. Conventional radiotherapy generally involves external beam radiotherapy; more recently, brachytherapy also is used, frequently as a boost treatment. Furthermore, IMRT is a newer form of radiation therapy intended to reduce its toxic effects, but its cost effectiveness has remained unclear [82]. Sheets et al. [61], using charts from 194 patients treated with radiation for SCCHN in a US hospital, calculated that IMRT was associated with significantly higher total (US\$5,881 increase) and treatment (US\$4,768 increase) costs than conventional radiotherapy (costing year NR). However, pretreatment costs were US\$1,700 lower with IMRT, and there was no difference in follow-up costs. Costs also increased with use of PET scans, recurrent disease, and patient comorbidities. Razfar et al. [82], using linked SEER–Medicare data, also compared IMRT with conventional radiotherapy and estimated that for oropharyngeal cancer, patients receiving IMRT cost Medicare US\$165,537, versus US\$87,922 for conventional radiotherapy (costing year NR). Early stage cancer treated with single modality therapy resulted in costs of US\$97,563 for IMRT and US\$63,374 for external beam radiotherapy. For advanced disease patients treated with surgery and radiation, IMRT cost US\$78,046 and conventional radiotherapy US\$52,034. Because of the expense but potential for lower morbidity with IMRT, both Sheets et al. and Razfar et al. [61, 82] recommend cost-effectiveness modeling as the next step in these comparisons.

3.6.4 Systemic Therapy

Two US studies [21, 31] and one from Greece [26] examined the costs of chemotherapy associated with certain combinations or settings. Crandley et al. [21] studied 65 consecutive patients treated at a US oncology center for oropharyngeal SCC, and reported that they incurred significantly higher charges to the hospital if docetaxel/cisplatin/5-fluorouracil (TPF) induction was added to their platinum chemoradiation (US\$189,321 with induction vs. US\$150,270 without it; costing year NR). A US trial randomized non-nasopharyngeal SCCHN patients to either inpatient or outpatient cisplatin, and recorded US\$18,664 higher costs over 6 months with inpatient administration (costing year NR) [31]. In Greece, a trial randomized 166 patients to one of two paclitaxel combinations, either with pegylated liposomal doxorubicin (PPLD) or gemcitabine (PGEM); PGEM cost significantly less (€7,419) than PPLD (€11,068) (2005 €) [26].

3.6.5 Multimodal Comparisons

Studies comparing costs among different modes of treatment examined patients in the USA, Spain, the Netherlands, Germany, and India. A study by Razfar et al. [81] using linked SEER–Medicare data evaluated per-patient costs associated with different multimodal treatment approaches, finding that surgery is significantly less expensive than radiation therapy with or without chemotherapy. Among 323 patients with T1–T3 laryngeal carcinoma, costs to Medicare of primary surgery totaled US\$50,444, significantly less than the US\$96,271 for conventional radiation therapy (costing year NR). In turn, conventional radiotherapy was much less expensive than IMRT (US\$199,661), and having no chemotherapy in the treatment regimen cost significantly less than including chemotherapy treatment (US\$64,512 vs. US\$233,582). Treatment with both IMRT and chemotherapy cost Medicare US\$334,754, compared with US\$146,442 for patients receiving other treatment. As above, with comparisons of IMRT versus conventional radiation, cost-effectiveness modeling is warranted to further understand whether potential lower morbidity with radiation instead of surgery is worth the increased costs [81].

In contrast to the US data, surgery was considerably more expensive than radiotherapy with or without chemotherapy in analyses conducted in the Netherlands, Germany, and Spain. In the Spanish study, laryngofissure cordectomy (€13,230) was more than double the cost of radiotherapy (€4,805) (costing year NR) [22]. Similarly, in the Dutch study, in which costs of diagnosis, treatment, follow-up, and complications were considered, surgery was associated with greater costs than radiotherapy, largely

driven by an increase in the number of inpatient days. The total mean cost per surviving disease-free patient after 1 year was €18,674 for external beam radiotherapy, €15,101 for brachytherapy, and €25,288 for surgery (2001 €) [46]. In addition, in Germany, costs for primary radiotherapy (€1,773) or CRT (€2,233) were minimal when compared with simple (€8,814) or elaborate (€22,298) surgery (2006 €) [52].

An attempt in rural India to determine whether multimodal therapy is feasible in that country, let alone cost effective, found that basic approaches may be possible [67, 93]. Most of the 230 patients presented to the cancer clinic with advanced disease and received multimodality treatment. Single modality treatment cost approximately 40,000 Indian rupees (INR), and multimodality treatment INR80,000 (costing year NR) [67, 93].

3.7 Cost Analyses: Treatment-Related Complications

In the current review, 20 publications from 19 studies described costs attributable to symptoms and side effects arising directly from the various treatments for HNC [11, 13, 15, 16, 25, 32, 36, 39, 42, 45, 47, 49, 50, 54, 59, 60, 73, 75, 76, 94]. The most commonly reported costs for treatment-related complications were due to infection [15, 16, 39, 45, 49, 59, 73] and surgical reconstruction following tumor resection [11, 36, 60, 75, 94]. Expenses for several other treatment-emergent side effects were noted, including peripheral neuropathy [50], dermatologic adverse drug reactions, acute mucositis [13, 25, 47, 54], osteoradionecrosis [76], and deep vein thrombosis or pulmonary embolism [32]. The majority of these studies ($n = 12$) evaluated economic data in the USA, and one economic analysis each was performed in the Netherlands [13], Canada [76], Finland [60], France [49], Ireland [73], and Taiwan [16].

3.7.1 Surgical Interventions

Four retrospective chart reviews, three conducted in the USA [11, 36, 75, 94] and one in Finland [60], assessed the costs of microsurgical free flap reconstruction in HNC and found that post-surgical or medical complications drive higher costs, especially in older patients and those who stay longer in an intensive care unit (ICU). A US study of 114 HNC patients reported that the average total cost of free flap surgical therapy was considerably greater (US\$54,702) for octogenarian patients compared with younger counterparts (US\$30,397) (costing year NR) [94]. This increase in cost largely resulted from greater pre-operative morbidity among the octogenarians, which more than quadrupled medical complications in this group (62 % of patients) compared with the younger patients (15 %). Increased

costs due to post-surgical complications also were identified in a study of 100 US HNC patients having microsurgical reconstruction. The average hospital length of stay nearly doubled for patients who experienced post-surgical complications, resulting in a 70.7 % increase (US\$20,292) in true costs compared with patients without additional complications. ICU costs (US\$1,956) accounted for a large component of this increased expenditure, especially in association with post-surgical complications (US\$9,760) [36]. Furthermore, a US study of 257 HNC patients who had undergone free flap surgery found that average cost per patient was increased by US\$3,238 when patients were cared for in the ICU versus a non-ICU setting following surgery [11, 75]. In the Finnish study, surgical complications nearly doubled costs, although this study only reported cost data separately for HNC patients in its abstract, limiting interpretation of the data [60].

3.7.2 Systemic Therapy

Two large US commercial database studies evaluated chemotherapy-associated peripheral neuropathy [50] and chemotherapy-related dermatologic side effects [54] and found that both conditions are associated with substantial economic burden. An analysis of a US commercial database reported that, compared with demographically matched controls without peripheral neuropathy, HNC patients with peripheral neuropathy have excess annual per patient healthcare costs of US\$36,660 (2006 US\$) [50]. Similarly, an analysis of another commercial database (2000–2010 US\$) identified higher costs for cetuximab-treated HNC patients who had experienced a dermatologic side effect ($n = 333$) versus those who had not ($n = 638$). Patients with a skin-related side effect incurred average monthly total healthcare costs of US\$12,539; those without a dermatologic side effect had costs of US\$9,684 (2010 US\$) [54]. After controlling for confounding factors, patients with skin-related side effects incurred a significant incremental total healthcare cost of US\$2,284 per patient per month, mainly due to an incremental inpatient cost of US\$1,702 per patient per month for those experiencing a dermatologic side effect.

3.7.3 Radiotherapy or Combined Chemoradiotherapy

A Dutch randomized controlled trial (RCT) [13], a Canadian retrospective chart review [76], and a US retrospective cohort database study [42] reported that costs associated with treatment-emergent side effects of radiotherapy or combined chemoradiotherapy (CRT) were considerable, and were driven in a large part by inpatient hospital admissions. Lang et al. [42] determined that mean per-patient costs associated with treatment-related side effects

were significantly higher for patients who received CRT (US\$15,825) than among those treated with radiotherapy alone (US\$6,223) (2006 US\$). Expenses for treatment-related side effects represented 17 % of total costs of treatment for patients who received combination therapy and 11 % of costs for those who received radiotherapy only, with hospital inpatient expenses comprising the largest cost component in both groups. Similarly, in the Dutch RCT, hospital admissions accounted for the majority (€3,013) of total average costs associated with chemoradiation toxicity (€3,789) [13]. The Canadian study specifically examined costs of surgical treatment of osteoradionecrosis of the mandible as a treatment-related side effect of radiotherapy in HNC patients. In this evaluation of 13 patients, the average cost per admission was C\$12,929, and total healthcare expenditure (16 admissions) was C\$206,860 [76].

Acute oral mucositis as a side effect of radiotherapy or radiochemotherapy was evaluated separately from other treatment-related complications in two US retrospective cohort studies, both of which determined that medical costs were higher for HNC patients who developed severe mucositis than for those who did not. In a US study of 204 patients, costs of oral mucositis increased with more severe disease; incremental costs were US\$1,700 for patients with grade 1–2, and US\$3,600 for patients with grade 3–4 oral mucositis (2006 US\$) [25]. Higher costs were reported in a US study of 99 HNC patients, 70.1 % of whom experienced severe mucositis/pharyngitis during radiochemotherapy. Incremental inpatient hospital costs for these patients were US\$14,000 and total medical costs were US\$17,244 (2005 US\$) [47].

3.7.4 Infection

Several studies in multiple countries examined costs due to infectious complications of treatment for HNC, including pneumonia and catheter-associated infection; all types of infection increased medical costs. A large US public database study found that for 123,662 HNC patients, vascular catheter-associated infection, while a rare complication, accounted for >70 % of all hospital-acquired conditions [39]. These infections accounted for a mean increase in surgical costs of US\$22,757 (2012 US\$). In addition, a recent cross-sectional study of 93,633 HNC patients treated surgically in the USA found that after controlling for other variables, urinary tract infection associated with peri-operative urinary catheterization significantly increased length of hospitalization and related costs (US\$14,992 increase) [15]. Similarly, a study of US Medicare claims data for HNC patients aged 65 years and older reported that serious fungal infections during hospitalization resulted in higher Medicare payments

(US\$25,942) for affected patients than for those without this condition (US\$10,131) (1998 US\$) [45]. It should be noted that lower reported costs in this latter study compared with others included in this review likely reflect the older costing year (1998), and the rising costs of healthcare in the intervening 15 years.

Post-treatment pneumonia was associated with increased medical costs in studies conducted in France, Taiwan, and the USA [16, 49, 59]. In the French prospective cohort study, post-operative pneumonia added €19,000 of direct medical costs to treatment. Patients who developed both surgical site infection and post-operative pneumonia had additional costs of €35,000 (2005 €) [49]. Similarly, in a retrospective claims analysis using Taiwan's National Health Insurance database, HNC patients with pneumonia following radiotherapy incurred an additional US\$11,612 in overall medical costs (approximately US\$188/day) (costing year NR) [16]. In addition, a large US database study concluded that infectious pneumonia increased hospital costs by US\$17,095, while aspiration pneumonia raised costs by US\$12,510 (2011 US\$) for HNC patients who developed these conditions [59].

Costs of antibiotic use to treat or prevent post-operative infection in HNC patients were assessed in two studies. A prospective study of 50 HNC patients in India reported that mean costs for use of a single antibiotic for prophylaxis were INR803, while those for use of combination antibiotic therapy were INR1,524 (costing year NR). Total cost for prophylaxis and post-operative treatment with antibiotics did not differ between the two regimens [48]. In a chart review of hospital data in Ireland, costs of the first hospital stay were more than three times higher in methicillin-resistant *Staphylococcus aureus* (MRSA)-positive patients than in MRSA-negative patients. Antibiotic costs were increased by 2,470 Irish pounds for HNC surgical patients treated for MRSA infection (costing year NR) [73].

3.8 Cost Analyses: Supportive and Palliative Care

Six studies in the USA, Korea, the Netherlands, and Australia [18, 19, 38, 41, 55, 57, 70] have examined costs associated with interventions related to nutritional support, post-treatment surveillance, and hospice or end-of-life care in HNC patients. Direct costs of these types of supportive and palliative care are minimal when compared with costs of treatment and expenditures for treatment-related side effects. However, it should be noted that there are no studies on palliative radiation, which may have higher costs than other forms of supportive care.

Two US database studies assessed supportive and palliative care incremental costs using Medicare claims data comparing HNC patients to demographically matched cancer-free controls [38, 41]. A high proportion of patients

with metastatic HNC (90.2 %) or recurrent HNC (71.0 %) received supportive care. For metastatic HNC patients, supportive care costs were US\$1,136 versus US\$20 in controls; for recurrent HNC patients, supportive care costs were lower (US\$342) than for metastatic HNC, but remained considerably higher than those for cancer-free controls (US\$24) (2008 US\$) [38]. Similarly, while only 14 % of HNC patients utilized hospice care, mean payments for this care were significantly higher for patients (US\$899) than for controls (US\$120) (1998 US\$) [41].

Costs of end-of-life care for HNC patients were further analyzed in a study of a US commercial claims database. These costs were assessed for patients diagnosed with advanced HNC between March 2003 and March 2008, comparing costs for the period prior to and following approval of cetuximab. Costs for end-of-life care were similar (US\$15,853 prior to approval, US\$21,822 following approval) for both groups [55].

An Australian RCT and a Korean RCT compared costs of two methods of providing nutritional support to HNC patients undergoing CRT or surgery; in both trials, nasogastric tube feeding was the less costly option. In the Australian trial, percutaneous endoscopic gastrostomy (PEG) tubes were nearly tenfold more costly than nasogastric tubes for nutritional support. This study examined 32 patients treated with PEG tubes and 73 with nasogastric tubes; the cost for PEG tubes was A\$736, while cost for nasogastric tubes was A\$76 (costing year NR) [18, 19]. The Korean trial compared nasogastric tube nutrition with total parenteral nutrition (TPN); the latter cost 11,810 Korean won (KRW) more per day. In addition, the initial device cost was more than tenfold higher for a central venous catheter for TPN (KRW24,210) than for a nasogastric tube (KRW3,510) (2007 KRW) [57].

A study of post-treatment surveillance in the Netherlands of patients with suspected recurrence of laryngeal cancer following radiotherapy found that ¹⁸F-deoxyglucose positron emission tomography (FDG-PET) scans resulted in cost savings over a direct laryngoscopy strategy. Using the results of the FDG-PET scan to select patients for laryngoscopy rather than performing this procedure on all patients led to mean cost savings of €399 (2003 €) with similar clinical outcomes [70].

3.9 Indirect Costs of HNC

Four studies identified by the current review reported high indirect costs associated with HNC [17, 65, 74, 80], particularly for the cost of patient time reduced workforce participation. A US study assessing the indirect costs of laryngeal cancer over a 12-month period found that each patient missed a mean 98 days from work. For the 35 patients assessed, short-term disability payments totaled

US\$361,730, and total lost wages in the 1-year period US\$556,955 (2008 US\$) [17]. A study using Norwegian population data to assess the impact of cancer on employment and earnings reported that HNC significantly lowered the odds of employment for men and women. It also significantly reduced earnings compared with the reference cancer-free population, by 17 % for men and 16.1 % for women [65]. Survey data collected from individuals with HNC in Ireland were combined with population-level survival estimates and national wage data to estimate the indirect costs associated with the disease. The average productivity losses per person attributable to temporary and permanent work absence and reduced work hours totaled €222,000 [80]. A US study of national patient time costs for HNC patients aged 65 years and older estimated that these costs in 2005 reached US\$101,187 [74]. For the initial phase of care, net patient time costs were US\$1,679 for hospitalizations, US\$146 for ambulatory physician visits, and US\$443–2,268 for other services (costing year NR). These costs tended to increase during the patients' last year of life, especially for hospitalizations [74].

4 Discussion

Studies assessing the full societal burden of HNC were not identified by this review; however, individual studies of overall national direct and indirect costs in the USA [85, 86] and in France [87] suggest that these components contribute nearly equally to the overall burden of disease. Very few studies reporting indirect costs of HNC were captured in this review, but of the four available, HNC appears to cause substantial work loss in the USA, Norway, and Ireland [17, 65, 74, 80]. Studies of direct medical costs of HNC have been dominated by US database studies, albeit with substantial heterogeneity in data sources and study designs that tends to thwart comparisons. Costs in linked SEER–Medicare data reflect the perspective of this US government program for insuring the elderly, who may have different costs and disease manifestations than working-age populations whose care is recorded in databases from private insurers. Given additional differences in time horizons (e.g., 6 months in one study, 5 years in another) as well as disease subpopulations (early disease in one study, metastatic HNC in another) and dates of diagnosis (the early 1990s in one study, the mid-2000s in another), it becomes impossible to compare or pool multiple studies to support a single estimate of a cost.

However, a clear general picture can emerge from the totality of the evidence, showing that this cancer presents a large economic burden to private and public payers in the USA, and from a smaller number of studies, payers in

Europe and elsewhere. More work is needed outside the USA, but in Europe and other regions, it is harder to find databases that are available to commercial sponsors of health economic research. Prospective studies would be a good alternative, and not many have been published in HNC. This has not changed since the review of the economics of HNC published in 2004 by Lee et al. [95], who noted a plethora of cost identification studies but very few with a prospective design. Adding economic endpoints to trials enrolling head and neck patients would be a good tack to take in any region. From the evidence currently available from the UK [37] and the Netherlands [69], forms of HNC present very high direct costs to these healthcare systems. It may be informative for future studies in Europe to focus on the costs of surgery; in contrast to the USA, surgical treatment appears substantially more expensive than radiotherapy with or without chemotherapy [22, 46, 52].

4.1 Low-Morbidity Techniques May Not Save Costs

In the USA, trends away from surgery may avoid associated morbidity, and the same is true for IMRT instead of conventional radiotherapy. However, these noninvasive/low-toxicity approaches do not necessarily lower total costs. A comparison in linked SEER–Medicare data by Razfar et al. [81] of surgery, radiation (IMRT or conventional), and chemotherapy found that for T1–T3 laryngeal carcinoma, surgery cost significantly less than any of the other modalities. Razfar et al. [82] also compared IMRT with conventional radiotherapy, as did Sheets et al. [61], and found significantly higher costs with IMRT. Cost-effectiveness modeling is needed to determine the value in quality-adjusted time of the added costs of these lower-morbidity approaches to HNC treatment. A recent German model determined that induction chemotherapy is cost effective in the treatment of operable advanced HNC [96]; similar strategies could be applied to analysis of other treatment options. In Europe, with surgery both more expensive and invasive than radiotherapy and chemotherapy, modeling should investigate whether its efficacy offsets these disadvantages.

4.2 Some HNC Costs to US Payers Have Risen Over the Last Decade

Some, but not all, costs of HNC appear to have risen over time in the USA. In a study by Reveles et al. [55] using commercial insurance claims, median total costs did not differ significantly between a cohort diagnosed with advanced SCCHN in 2003–2006 and a cohort diagnosed in 2006–2008. However, diagnostic costs rose significantly after 2006. Maddox and Davies [44], using a database of

US hospital discharges, calculated that mean hospital charges per patient for laryngectomies nearly doubled from 1997 to 2008 in constant 2008 dollars. However, a trend toward less use of surgery over the same period meant that only half as many laryngectomies were performed in 2008 compared with 1997. These types of large, structural changes in healthcare delivery may contribute to the recent slowdown in US spending on healthcare, which at present is only rising at approximately the rate of inflation. Spending is currently forecast to increase in 2014 and beyond with an aging population, an improved economy, and passage of the *Affordable Care Act* [97].

4.3 Limitations

Chief among the limitations of the current review is that it includes only studies that assessed and reported original costs. It therefore omits nearly all models and systematic reviews, which use secondary cost data. Studies reporting original data are usually retrospective database analyses, especially in the USA, so it is also important to note that databases are not a good source of information about tumor stage and location. For analyses of the influence of stage and location on cost, chart reviews will be more likely to yield usable information. Other limitations of the current review are that it is limited to English-language literature, and that it omits US studies of real-world cetuximab costs for late stage HNC, as the 2011 approval of cetuximab for metastatic/recurrent HNC in the USA would have been too recent for even 2013 publications to have assessed an adequate sample and timeframe.

4.4 Next Steps

The best next step would be to review models and other studies using secondary data, identify gaps in understanding of both original and modeled economic burden, and then use the current review of original costs to derive data for the next set of models. This would include published data but also identification of databases that have yielded sufficient cost information regarding this cancer. A new look at databases or charts, especially in Europe or other areas outside the USA, will also yield retrospective data on costs of recent developments such as cetuximab, as well as HPV vaccines [98]. Because this review is limited by the fact that approximately 90 % of reviewed studies do not report cost data by HNC tumor site, and even fewer report cost data by tumor stage, we recommend that (as possible) future analyses consider reporting care and associated costs by specific HNC tumor site as well as by tumor stage. Taken together, these efforts to gain a greater understanding of the economic burden of this cancer will

improve the ability of healthcare systems to prioritize and select forms of care that are both effective and affordable.

5 Conclusions

Studies have not addressed the societal burden of HNC, but evidence from the USA and France suggests approximately equivalent direct and indirect costs to these countries. Most studies of direct medical costs have used US databases of claims to public and private payers; in the USA, excess costs to these payers were estimated to be US\$8.5 billion in 2008. In the UK, costs to the NHS totaled £255 million over a possible 5 years following resection. Costs appear higher for patients with metastatic/recurrent disease, those undergoing surgery and during the first year afterward, and US patients insured by private payers. Indirect costs measured in the USA, Norway, and Ireland indicate that HNC causes substantial work loss in these countries. More work is needed in Europe and other regions outside the USA, in addition to prospective cost-identification studies and evaluations of the costs of surgery in Europe.

Acknowledgments This research was funded in part by Boehringer Ingelheim International GmbH. The authors have no conflicts of interest relevant to the content of this report, and the opinions expressed herein are those of the authors. Dr. Chris Pashos, as corresponding author, takes responsibility for the scientific content of the study. The authors acknowledge the valuable contributions of Amy McDonough and Karin Travers, who assisted with data collection, and Tiffany Pokora, who provided project management assistance.

Author contributions All authors were involved in conception and planning of the systematic review. TF and EW interpreted and synthesized the results of the review and drafted the paper. IG, JL, and CP contributed to critical review and revisions of drafts. All authors approved the final submitted version of the manuscript.

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