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Direct health-care cost of head and neck cancers: a population-based study in north-eastern Italy

Jerry Polesel[1] · Valentina Lupato[2] · Paolo Collarile[3,8] · Emanuela Vaccher[4] · Giuseppe Fanetti[5] · Vittorio Giacomarra[2] · Elisa Palazzari[5] · Carlo Furlan[6] · Fabio Matrone[5] · Federico Navarria[5] · Carlo Gobitti[5] · Emilio Minatel[5] · Diego Serraino[1] · Silvia Birri[7] · Giovanni Franchin[5]

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Abstract

Improvements in prognosis of head-and-neck squamous cell carcinoma (HNSCC) have paralleled with an increase in health-care costs, so that an economic evaluation is of growing importance. Presently, most of the evidence is from insurance-based studies in the USA. Between 2007 and 2010, 879 HNSCC patients were identified through the population-based cancer registry of the Friuli Venezia Giulia region, including 266 oral, 187 oropharyngeal, 136 hypopharyngeal, and 290 laryngeal cancers. Health-care costs from diagnosis to treatment initiation and in the following 2 years were retrieved through a record linkage with the regional health data warehouse. This database collected comprehensive health information on all resident citizens. Generalized linear models with a gamma distribution and log-link function were applied to model costs. The average health-care cost from diagnosis up to 2 years after treatment initiation was €20,184 (95% confidence interval: €19,634 – 20,733). Heterogeneity emerged according to cancer site, elective treatment, and retreatment for cancer persistence/recurrence (no: €13,896; yes: €24,599; $p < 0.001$). An advanced stage was associated with increased costs stage (I: €12,969; II: €18,276; III: €26,229; IV: €25,574; $p < 0.001$) as the result of treatment complexity and elevated frequency of patients retreatment due to recurrence. These findings further support strategies to diagnose patients at an earlier cancer stage and the accurate definition of diagnostic and treatment pathways, to start treating patients when radical unimodal approach is still feasible. Besides the advantage in prognosis due to timely curative treatments, this would reduce the economic burden of cancer treatment.

Keywords Head and neck cancer · Economic burden · Treatment cost · Diagnostic cost · Population-based study

Introduction

The treatment approach of head and neck squamous cell carcinoma (HNSCC) has changed in the last decades, due to technological progresses in radiotherapy, to the development of new chemotherapy agents, and to the advancements of surgical techniques. Improvements in the prognosis and in the quality of life of HNSCC patients have paralleled with an increase in the economic burden of HNSCC on the health system. Therefore, the estimate of health-care cost of HNSCC patients is of great interest nowadays for sound decision-making in allocation of limited resources to provide the best care in an economically sustainable context [1]. Although patient's clinical benefit must remain the primary aim in choosing the best available treatment, the evaluation of disease economic burden is of primary interest to address funds allocation when resources are limited and patients' needs are competing.

The economic burden of HNSCC has been evaluated by several studies [1–6], mostly from the USA. Worldwide, studies generally showed great variability in health-care costs, ranging from roughly €3000 to €67,000 in the first year after diagnosis, as the results of heterogeneity in the investigation protocols. Indeed, costs depend on the definition of the target population and on the inclusion of direct costs (i.e., those directly associated with cancer diagnosis and treatment), or indirect ones (such as loss of productivity

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✉ Jerry Polesel
polesel@cro.it

Extended author information available on the last page of the article

and premature mortality) in the calculation. Further, the economic development level of the Country varies across geographic areas, as well as the rate of contribution of public and private providers to the Health Service. None of these studies was conducted in Italy.

In Italy, the National Health Service with universal coverage is largely funded by the central government, which controls the distribution of tax revenues to guarantee a core benefit package of health services for all residents in the Country [7]. The 20 Italian regional authorities have the responsibility to organize and deliver health services through local health units, and they may economically contribute to the national resources. Health services are charged on the National Health System according to Diagnosis-Related Group (DRG) tariffs. Private health insurance plays a limited role in the health system—including north-eastern Italy—accounting for about 1% of total spending [7].

We conducted a retrospective population-based study, using data from an administrative database, to estimate the direct health-care cost of HNSCC in the north-eastern part of Italy. The determinants of health-care costs were further investigated, with a focus on treatment approach and on cost evaluation according to time since treatment initiation.

Materials and methods

Since 1995, the population-based Friuli Venezia Giulia Cancer Registry (FVG-CR) has been collecting data on newly diagnosed cancers in people living in the Friuli Venezia Giulia region, north-eastern Italy. FVG-CR covers approximately 1.2 million inhabitants, registering data with high standards of completeness and quality [8].

The present analysis included invasive squamous cell carcinomas (ICD-O-3 morphology codes: 8000–8082, 8430, 8480) of the oral cavity (ICD-10: C00.3–C00.9, C02–C06, C14), oropharynx (C01, C09–C10), hypopharynx (C13), and larynx (C32) diagnosed between January 2007 and December 2010. Overall, 1216 patients were identified through FVG-CR. The analysis was restricted to patients who were likely to have received treatment with curative intent. Therefore, we excluded 16 patients diagnosed on death certificate only and 134 patients who did not undergo any treatment; we further excluded 187 HNSCCs diagnosed in patients aged above 75 years of age who were likely to have received palliative treatment because of older age, thus leaving 879 cases available for the present analysis. Almost all cases (99.0%) were pathologically confirmed, whereas the remaining ones were diagnosed on cytology. Although the majority of patients were staged for clinical purpose, complete TNM staging was recorded in FVG-CR only for 292 (33.2%) cancer patients.

Health data were retrieved from the Regional Health Data Warehouse (RHDW), a database collecting comprehensive health information on people living in the Region. RHDW included individual information on patients' mobility, hospital admissions and discharges, pathological records, treatments, diagnostic procedures, and drug prescriptions. For administrative aims, the RHDW recorded all the costs, according to DRG tariffs, charged to the health-care system for any inpatient and outpatient health service provided by the Health Service to residents through either public or private accredited providers. No tariffs modification was appreciable in the study period; for comparisons with literature data, costs were actualized to 2010. In full compliance with national and local confidentiality laws and regulations, personal identifiers were removed from all records; record linkage was possible through an anonymous identification code.

For each patient, index date was defined as the date of the earliest elective treatment (surgery, radiotherapy, or chemotherapy) for HNSCC. Cost related to HNSCC treatment was retrieved from cancer diagnosis to index date (pre-treatment period) up to 24 months after index date. A cost was considered related to HNSCC when it met at least one of the following conditions: (a) HNSCC was mentioned among the diseases responsible for hospital admission; (b) surgery, radiotherapy (RT) or chemotherapy for HNSCC; (c) reconstructive surgery including the respiratory tract, oral cavity, pharynx, larynx, or soft tissues or bones of the skull; (d) imaging including head, neck, or chest; (e) antiblastic drugs specific for HNSCC; (f) drugs used in supportive care for HNSCC.

Treatments (i.e., surgery, RT, and chemotherapy) were identified using ICD9-CM codes for diagnosis and procedures recorded in records from hospital discharge from out-patients health services. Elective surgery was defined as surgical treatment without any mention of radio- or chemotherapy before surgery or in the 90 days after surgery. Elective RT was defined as RT without any mention of surgery or chemotherapy before RT initiation or in the 4 months (122 days) thereafter. Elective radiochemotherapy (RCT) was defined as radio- and chemotherapy without any mention of surgery before RCT initiation or in the 4 months (122 days) thereafter. Adjuvant RCT was defined as radio- or chemotherapy within 90 days from surgery. Any treatment (surgery, chemo- or radiotherapy) beyond the above-defined time windows was considered as a retreatment for cancer persistence or recurrence. A sensitivity analysis was conducted, modifying the time limits by 5 or 10 days, with no appreciable modification. To account for general socio-economic characteristics, deprivation index was associated with each patients according to the place of residence [9]. Briefly, this index combined five indicators of social and material deprivation in the municipality of residence, namely low education, unemployment, non-homeownership, single-parent family, and high-population density: higher the index, higher the deprivation of the place of living [9].

Total cost from diagnosis up to 2 years following initial treatment was calculated as the sum of all HNSCC related costs. To account for the non-normal distribution of cost data, generalized linear models with a gamma distribution and log-link function were applied to model costs [10], including the following variables as covariates: sex, age at cancer diagnosis, cancer site, and elective treatment. The statistical difference in mean of predicted costs across strata was evaluated through the analysis of variance (ANOVA).

Costs were further analyzed according to phases, defined according to time to treatment initiation as follows: pre-treatment (i.e., from cancer diagnosis to treatment initiation); 0–3 months; 4–12 months; and 13–24 months. To account for patients survival, the cost of each phase is weighted for probability of being alive at the beginning of the phase and then sum up to the total [11]. Statistical analysis was performed using SAS 9.4, and significance was claimed for $p < 0.05$ (two-sided).

Results

Overall, 879 cancer patients were identified, including 266 oral, 187 oropharyngeal, 136 hypopharyngeal, and 290 laryngeal cancers (Supplementary Table 1). As expected, elective treatment was associated with cancer site; surgery was the most frequent treatment for cancer of the oral cavity (58%) and larynx (46%), whereas RCT was predominant for cancer of the hypopharynx (71%) and oropharynx (56%). Prognosis was also different across cancer sites; retreatment for cancer persistence/progression was more frequent for hypopharyngeal (73%) and oropharyngeal cancers (65%), impacting on cancer lethality (46% and 41% for hypopharyngeal and oropharyngeal cancer, respectively).

The average health-care cost from diagnosis up to 2 years after treatment initiation was €20,184 (95% CI €19,634 – 20,733—Table 1), for a total of more than €4.4 million/year. The cost was similar between sexes, and it increased with increasing deprivation index (from €18,529 to €21,910 in low and high deprivation index, respectively; p-trend = 0.01). Costs varied significantly according to cancer site, elective treatment, and cancer retreatment ($p < 0.001$). Results were confirmed in the subset of 292 patients with available TNM staging (Supplementary Table 2); further, this analysis revealed a lower cost for stage I (€12,958) than for stage III–IV cancers (approximately €26,000; $p < 0.01$) .

Overall, the pre-treatment cost was approximately €2000; the cost peaked in the period 0–3 months from initial treatment (€11,074; 95% CI €10,810–11,338) and progressively declined thereafter (Table 2). This pattern was similar for all cancer sites but hypopharynx, where costs remained quite elevated also 4–12 months (€10,338) and 13–24 months after index date (€7314). The pattern of cost greatly differed according to elective treatment. Surgery and adjuvant RCT showed the lowest pre-treatment cost (€906 and €815, respectively), followed by the steepest increase in the

Table 1 Distribution of 879 patients with head and neck cancer and predicted costs[a] in the 24 months following treatment initiation,[b] according to socio-demographic characteristics and clinical data

Characteristics	*N*	Cost (€)	95% CI (€)	ANOVA
All	879	20,184	19,634–20,733	
Sex				
Man	710	20,082	19,454–20,709	$P = 0.45$
Woman	169	20,614	19,497–21,731	
Age (years)				
18–54	181	22,315	21,032–23,598	$P < 0.01$[d]
55–59	165	21,649	20,404–22,895	
60–64	168	20,049	18,764–21,333	
65–69	197	20,152	19,026–21,277	
70–75	168	16,622	15,555–17,690	
Year of cancer diagnosis				
2007	233	21,078	20,016–22,140	$P = 0.07$[d]
2008	199	19,541	18,436–20,645	
2009	232	21,315	20,181–22,449	
2010	215	18,590	17,520–19,660	
Deprivation index[c]				
High	293	21,910	20,900–22,919	$P = 0.01$[d]
Medium	297	20,092	19,165–21,019	
Low	289	18,529	17,644–19,414	
Previous cancer				
No	593	20,368	19,694–21,045	$P = 0.34$
Yes	286	19,796	18,851–20,746	
Cancer site				
Oral cavity	266	18,462	17,720–19,205	$P < 0.01$
Oropharynx	187	24,253	23,197–25,310	
Hypopharynx	136	28,011	26,620–29,402	
Larynx	290	15,469	14,701–16,236	
Elective treatment				
Surgery	341	16,940	16,415–17,466	$P < 0.001$
RT	112	9116	8657–9574	
RCT	316	26,127	25,274–26,980	
Adjuvant RCT	110	24,436	23,547–25,325	
Retreatment within 24 months				
No	369	13,665	13,180–14,149	$P < 0.001$
Yes	510	24,901	24,288–25,513	

RT radiotherapy, *RCT* radiochemotherapy

[a]Costs were estimated through generalized linear models with a gamma distribution and log-link function including all the variables in the table

[b]Including costs from cancer diagnosis to treatment initiation

[c]Deprivation index was defined as high, medium, and low according to tertiles

[d]*P* from ANOVA with contrasts for trend

Table 2 Distribution of costs[a] by time from treatment initiation according to cancer site and treatment

Cancer site/treatment	Before treatment		Time from treatment initiation					
			0–3 months		4–12 months		13–24 months	
	Cost (€)	95% CI (€)	Cost (€)	95% CI (€)	Cost (€)	95% CI (€)	Cost (€)	95% CI (€)
All	2023	1917–2130	11,074	10,810–11,338	5600	5183–6016	3291	3075–3506
Cancer site								
Oral cavity	1223	1103–1343	11,102	10,702–11,503	4421	3838–5004	2282	2071–2493
Oropharynx	2932	2640–3223	12,646	12,123–13,170	8658	7562–9754	4113	3696–4531
Hypopharynx	2809	2521–3096	12,833	12,227–13,438	10,338	9076–11,600	7314	6523–8105
Larynx	1803	1659–1948	9209	8729–9689	2664	2294–3035	2131	1918–2345
Elective treatment								
Surgery	936	883–988	11,170	10,943–11,396	2176	1996–2355	2481	2261–2701
RT	2738	2535–2941	3665	3529–3801	2015	1619–2410	1621	1262–1981
RCT	3365	3182–3548	11,730	10,744–12,717	11,634	10,819–12,448	5172	4643–5702
Adjuvant RCT	815	737–894	16,365	15,752–16,979	3955	3708–4202	3412	3082–3742

RT radiotherapy, *RCT* radiochemotherapy

[a]Costs were estimated through generalized linear models with a gamma distribution and log-link function including all the variables in Table 1

0–3-month period. Conversely, detailed imaging, simulation, and treatment preparation required by RT increased pre-treatment cost for RT and RCT at approximately €3000. RT showed slight variation over the period under investigation. Conversely, RCT costs peaked in the period 0–3 months and remained elevated for the 12 months after treatment initiation.

Patients retreatment greatly impacted on overall costs and its frequency differed across cancer sites (Supplementary Table 1) and treatment approaches (66% of patients treated with surgery or RCT compared with 31% in patients undergoing RT). Therefore, analyses were further stratified by patient retreatment (Fig. 1): as expected, patients retreatment had no influence on cost up to 3 months after treatment initiation, but greatly increased treatment costs for every cancer sites and elective treatment. The impact of cancer retreatment on overall costs was greater for RT (from €7988 to €17,759: + 122%) due to salvage surgery (Fig. 1b). The impact of retreatment was milder for surgery (+ 56%), RCT (+ 33%), or adjuvant RCT (+ 32%).

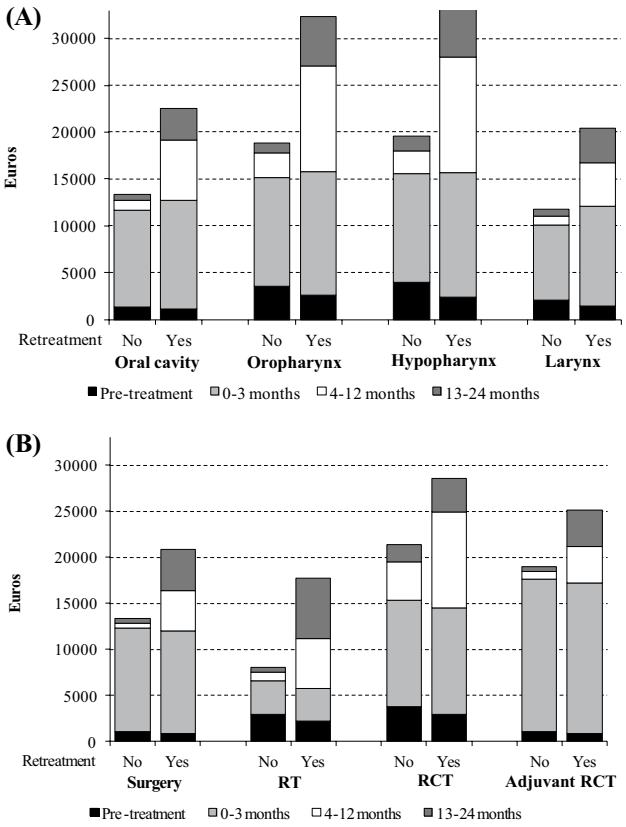

Fig. 1 Estimated costs by time from treatment initiation according to cancer site (**a**) and elective treatment (**b**), stratified by patient retreatment for cancer persistence/recurrence. *RT* radiotherapy, *RCT* radiochemotherapy

Discussion

The study findings indicate that, in the first 2 years of treatment, the care of HNSCC patients requires approximately €20,000. Such cost is concentrated mainly in the first year, and a substantial heterogeneity emerged according to cancer site, stage, and elective treatment. Study results were strengthened by the utilization of population-based databases: information bias was minimized and representativeness of health-care cost estimates was improved.

Differences in national health services in various countries, in addition to a lack of studies at population level in countries with universalistic health systems such as Italy, prevent international comparisons. Moreover, current literature has reported heterogeneous estimates as a consequence of differences in patients' selection, treatment setting, calendar period, time window of cost estimation, and statistical methods [1–6]. The majority of the studies were from the USA, thus based on claims of private and public payers [2, 4–6], while only very few study were conducted in Europe. Results similar to the present study were reported by an early investigation conducted in the Netherlands [12] on head and neck cancer patients treated between 1994 and 1996 in two major university hospitals: in the first 2 years of treatment the total cost was €21,585 (approximately €29,000 in 2010). Likewise, a recent study [13], conducted in the UK on HNSCC patients who had undergone surgery between 2003 and 2008, estimated a cost of about €23,500 (approximately €25,200 in 2010) in the first two years after surgery. Cost estimates were lower in 95 Greek oral cancer patients treated between 1993 and 1999 [14], reporting €8450 (approximately €11,200 in 2010) from diagnosis up to 3 years later.

As expected, cancer characteristics (e.g., site and stage) and therapeutic variables (e.g., elective treatment and patients retreatment) were major determinants of HNSCC cost. Differences by cancer site were largely attributable to diverse elective treatments; indeed, cancer of the oropharynx and hypopharynx—the most expensive cancer sites—was predominantly treated through RCT, whereas 58% of oral cancers underwent surgery. It is further likely that the access to expensive high-technology facilities is different according to cancer site. A SEER-Medicare examining radiotherapy use in non-metastatic HNSCCs [15] reported that the chance of receiving intensity-modulated radiotherapy (IMRT) versus conventional RT significantly varied according to cancer site and stage. This directly impacted on the heterogeneity of costs since the mean cost of IMRT was much higher than conventional RT ($101,099 and $42,843, respectively).

A direct association of costs with increasing stage has been consistently reported [2, 14, 16], largely attributable to treatment complexity in more advanced cancers. Patients with early stage HNSCC usually require conservative treatments, often unimodal [17], and have low probability of cancer recurrence. It is therefore clear that, beside shortening time to treatment initiation [18] and improving patients' quality of life, early diagnosis will reduce treatment costs.

In the present study, we highlighted the impact of retreatment on total health-care cost, which is not surprising, since patients with successful elective treatment usually require only surveillance costs. Conversely, patients with persistent/recurrent diseases underwent additional treatments: retreatment costs were greater for patients initially treated with RT, who usually underwent salvage surgery.

Finally, socioeconomic deprivation was significantly associated with health-care cost. HNSCC patients resident in deprived areas were reported to be diagnosed at later cancer stages than people living in affluent areas [19], thus requiring more intense treatment.

The cohort definition through complete and validated cancer information from a population-based cancer registry [8] is a major strength of this study. All cancer cases diagnosed in the Friuli Venezia Giulia region in the period under investigation were considered for the present study, minimizing selection bias. Further, cancer registry information on topography and staging were validated according to international rules [8], thus strengthening the analysis by cancer site, which were seldom reported in previous studies [4].

Information bias is a major concern in our study. Cost data were derived from the RHDW, a database originally set up for administrative aims, including the control of healthcare resource use. The DRG reimbursement system may lead to bias in individual estimation of health-care expenditure, since the claimed amount did not consider all the health services provided to the patients during hospital admission. Nonetheless, DRG represented the actual cost charged to the healthcare system by health providers, thus offering the most reliable information on resource demand in the Italian Health System. Further, treatments were defined through RHDW patients records; it is therefore possible that misclassification may have occurred. To reduce bias due to sub-optimal treatment in elderly, patients aged ≥ 75 years were excluded. The lack of staging for the majority of cases is a main weakness. Nonetheless, we performed a sensitivity analysis on patients with TNM stage, showing that cost patterns did not substantially change in this subgroup after adjustment for TNM stage, reassuring about the reliability of the overall study results.

The present study provided estimates of HNSCC healthcare cost in the context of universalistic health system financed by public resources. These findings further support strategies to diagnose patients at an earlier cancer stage and the accurate definition of diagnostic and treatment pathways, to start treating patients when radical unimodal approach is still feasible. Besides the advantage in survival and disease-free survival due to timely curative treatments [17], this would reduce the economic burden of cancer treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Affiliations

Jerry Polesel[1] · Valentina Lupato[2] · Paolo Collarile[3,8] · Emanuela Vaccher[4] · Giuseppe Fanetti[5] · Vittorio Giacomarra[2] · Elisa Palazzari[5] · Carlo Furlan[6] · Fabio Matrone[5] · Federico Navarria[5] · Carlo Gobitti[5] · Emilio Minatel[5] · Diego Serraino[1] · Silvia Birri[7] · Giovanni Franchin[5]

Paolo Collarile
paolo.collarile@aas3.sanita.fvg.it

[1] Unit of Cancer Epidemiology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, via Gallini 2, 33081 Aviano, PN, Italy

[2] Unit of Otorhinolaryngology, Santa Maria degli Angeli General Hospital, via Montereale 24, 33170 Pordenone, PN, Italy

[3] Friuli Venezia Giulia Cancer Registry, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, via Gallini 2, 33081 Aviano, PN, Italy

[4] Unit of Medical Oncology A, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, via Gallini 2, 33081 Aviano, PN, Italy

[5] Unit of Radiatherapic Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, via Gallini 2, 33081 Aviano, PN, Italy

[6] Unit of Radiotherapy, San Martino Hospital, Viale Europa 22, 32100 Belluno, BL, Italy

[7] Unit of Epidemiology, AAS 5 "Friuli Occidentale", via della Vecchia Ceramica 1, 33170 Pordenone, PN, Italy

[8] Present Address: Unit of Hygiene and Public Healtlh, Department of Prevention, AAS3 "Alto Friuli-Collinare- Medio Friuli", Via Duodo 82, 33033 Codroipo, UD, Italy