CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Did the addition of concomitant chemotherapy to radiotherapy improve outcomes in hypopharyngeal cancer? A population-based study

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ABSTRACT

Background For oncologists and for patients, no site-specific clinical trial evidence has emerged for the use of concurrent chemotherapy with radiotherapy (CCRT) over radiotherapy (RT) alone for cancer of the hypopharynx (HPC) or for other human papilloma virus–negative head-and-neck cancers.

Methods This retrospective population-based cohort study using administrative data compared treatments over time (1990–2000 vs. 2000–2010), treatment outcomes, and outcomes over time in 1333 cases of HPC diagnosed in Ontario between January 1990 and December 2010.

Results The incidence of HPC is declining; the use of CCRT that began in 2001 is increasing; and the 3-year overall survival for all patients remains poor at 34.6%. No difference in overall survival was observed in a comparison of patients treated in the decade before CCRT and of patients treated in the decade during the uptake of CCRT.

Conclusions The addition of CCRT to the armamentarium of treatment options for oncologists treating head-and-neck patients did not improve outcomes for HPC at the population level.

Key Words Hypopharyngeal cancer, chemoradiotherapy, outcomes, population-based studies

Curr Oncol. 2016 Aug;23(4):266-272 www.current-oncology.com

INTRODUCTION

Squamous cell carcinoma of the hypopharynx (HPC) is the least common of the upper aerodigestive cancers, representing 5% of head-and neck-cancers[1]. Because of factors such as advanced disease, patient comorbidity, and a high incidence of distant metastases[1–4], patients with HPC have the worst prognosis of all head-and-neck cancer patients, with a 28% 3-year overall survival (OS) and a 37% 5-year disease-specific survival (DSS). Hypopharyngeal cancer is most common in men in their mid-60s and with a lower socioeconomic status. It is caused by alcohol or smoking (or both) and is not commonly associated with human papilloma virus (HPV), presumably because of the lack of lymphoid tissue in the hypopharynx. Studies by Joo *et al.*[5], Wendt *et al.*[6], Wilson *et al.*[7], and Lewis *et al.*[8] reported a low proportion (0%–11%) of p16 HPV-positive tumours in patients with HPC.

Treatment has varied over time and between jurisdictions, but essentially, until the late 1990s, the typical treatments were RT, surgery, or a combination of the two, with no evidence of the superiority of one treatment modality for all cases[9]. With the advent, based on randomized trials and meta-analyses[10–13], of concomitant chemoradiotherapy (CCRT) for head-and-neck squamous cell carcinomas, patients since the late 1990s have been offered CCRT regimens, although there is little evidence that CCRT offers improved outcomes over RT alone for HPV-negative patients because the clinical trials did not control for HPV. As oncologists have moved more toward the concept of organ preservation, other treatments have included induction chemoradiotherapy[3,14,15] and transoral laser surgery[16,17]. There is also considerable parallel evidence that the addition of chemotherapy to RT increases acute and late toxicity[18–22], creating clinical problems that can be particularly severe in this patient population[21]. A complete review of treatment

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options published by Takes *et al.*[23] concluded that more evidence was needed to determine optimal treatment and that "treatments should be individualized by knowledgeable multidisciplinary teams."

The objectives of the present study were to describe the evolution of treatments for HPC between 1990 and 2010 across Ontario and to compare multiple outcomes by treatment era for a complete population of patients.

METHODS

Data Sources

The Ontario Cancer Registry (OCR) is a population-based cancer registry that captures information on all incident cases of cancer in Ontario. It is based on pathology reports abstracted at the OCR, electronic records submitted from the regional cancer centres, hospital discharge records, and reports of deaths from the Registrar General of Ontario. The OCR includes patient demographics, date of diagnosis, vital status, and inpatient hospital procedures received.

The Oncology Patient Information System was created by Cancer Care Ontario; it is the common electronic patient database used by all Ontario cancer centres and Princess Margaret Hospital. The data include a Radiation Planning/Treatment Activity section and a Systemic Drug Delivery Event section. Using those sources, RT data (intent, dose, frequency, and dates) and chemotherapy dates were obtained.

The Ontario Health Insurance Plan database contains data on the fee-for-service claims paid by the universal health care system.

The Discharge Abstract Database maintained by the Canadian Institute for Health Information contains information on all hospital discharges, including those after surgery (laryngectomy).

Dataset Creation

The initial dataset was created at the Division of Cancer Care and Epidemiology of Queen's University. It included OCR data for HPC patients (*International Statistical Classification of Diseases and Related Health Problems,* version 9, codes 148.0–148.9)—that is, demographics, hospitalizations, and vital status—and the Oncology Patient Information System (cancer treatment). The dataset was then migrated to the Institute for Clinical Evaluative Sciences (ICES) for linkages to the Discharge Abstract Database (hospitalizations, treatments, and outcomes) and the Ontario Health Insurance Plan (billing data for surgery, RT, chemotherapy, and other procedures), thus creating the clinical story for each anonymized patient. As an independent, non-profit research organization, ICES is funded by the Ontario Ministry of Health and Long-Term Care. To protect the privacy of personal health information, datasets relating to 5 or fewer subjects cannot be reported.

Setting

In Ontario, all HPC patients were treated at 1 of 8 regional head-and-neck cancer treatment centres, including Princess Margaret Hospital, that are located at major teaching hospitals. The hospitals and cancer centres are staffed by experienced surgical, radiation, and medical oncologists, and all patients were reviewed at multidisciplinary tumour boards.

Variables

Comorbidity was established using the Elixhauser index[24–26], based on a 5-year "look-back" at hospitalizations. Elixhauser created a summative scale based on 30 domains, and we used the cut-points of 0, 1, 2, and more than 2[24,27], with greater comorbidity resulting in a higher score.

Socioeconomic Status

Income quintile for the neighbourhood of each patient was obtained (the higher the quintile, the higher the neighbourhood income).

Clinical Stage

The TNM category and stage information for head-and-neck cancers were not being submitted to the OCR by hospitals or cancer centres during the period of the present study and thus were unavailable.

Vital status and cause of death were obtained from the Ontario Registrar General up to 31 December 2012.

Initial Treatment

Primary surgery (with or without RT) was defined as any of laryngectomy, laryngopharyngectomy, or partial pharyngectomy (with or without neck dissection) performed within 4 months of diagnosis, with or without postoperative RT delivered within 4 months of surgery. The choice of 4 months was made to include patients with residual disease, because salvage RT would be considered part of the treatment plan. Treatments after 4 months, including subsequent laryngectomy, were assumed to be for the management of recurrent disease.

Primary RT (with or without surgery) was defined as receipt of more than 20 fractions or more than 5000 cGy (or both) starting within 4 months of diagnosis, with or without pre-RT neck dissection, and with or without surgery to the primary or the neck within 4 months of RT completion. Treatment with more than 20 fractions or 5000 cGy (or both) was defined as curative because less than 20 fractions or 5000 cGy would constitute palliative treatment.

The use of CCRT (with or without surgery) was defined as more than 20 fractions or more than 5000 cGy (or both) with either a record of chemotherapy started within 30 days of the start of RT or finished within 30 days of RT completion. The CCRT group also included patients receiving pre-RT neck dissection or surgery to the primary or the neck within 4 months after RT completion.

Surgery plus CCRT was defined as surgery as already described, with CCRT starting within 4 months after surgery.

Induction chemotherapy with RT was defined chemotherapy beginning and ending before the start of RT, with or without surgery to the primary or the neck within 4 months after RT completion.

"No treatment" included palliative treatments (any treatment starting more than 4 months after diagnosis; RT using less than 20 fractions or less than 5000 cGy, or both) and patient records having incomplete data and from which treatments could not be determined.

"Other treatment" included other combinations or sequences of treatments.

Analysis

The results of treatments were assessed by comparing outcomes for all patients receiving those treatment types by era (1 January 1990 to 31 January 1999, 1 January 2000 to 31 January 2010) and then for all patients by treatment type.

The os and laryngectomy-free survival (LFS) are reported using the Kaplan–Meier method with log-rank tests. Laryngoesophageal dysfunction-free survival (LEDFS)[28] was based on os without laryngectomy at 2 years and the absence of a billing code for either a tracheotomy tube change or a gastrostomy tube change between the 2nd and 3rd years of follow-up. Cox proportional hazards regression was used to model outcomes with respect to variables, yielding hazard ratios (HRS), 95% confidence intervals (CIS), and *p* values.

RESULTS

Between 1 January 1990 and 31 January 2010, 1333 patients 35–75 years of age with a diagnosis of squamous cell HPC were identified. Average age in the cohort was 62.4 years, 60% had pyriform fossa cancers, more than 30% of patients had significant comorbidity, and 50% resided in neighbourhoods reflecting the lowest two income quartiles (Table I). The lateral wall sub-site has no assigned *International Statistical Classification of Diseases and Related Health Problems* code, and so could not be included. When patients were compared by treatment era (pre-2000 and post-2000), no change was observed in the distributions of age, sex, and comorbidity ($p = 0.92, 0.28, 0.44$ respectively).

Figure 1 demonstrates the declining incidence of HPC over time, consistent with other studies[29–32].

The lower panel of Figure 2 presents the treatment profile for the patient cohort during each successive year in Ontario. The treatment proportions in each year reflect all treatment centres; however, both the RT and the chemotherapy data for 1 centre were not available for 2005–2007. If treatment could not be assigned for each of a centre's patients using other data sources or variables, those patients were assigned to the "no treatment" group, which included patients who received no treatment, palliative treatment, or noncurative treatment, or who were treated but whose records were incomplete or lacked treatment data. As can be seen in Table II, treatment evolved (which was expected), with a progressive increase in the number of patients receiving CCRT and fewer patients receiving RT alone or primary surgery after 2001.

The upper panel of Figure 2 presents the 3-year os for the group of patients treated in each year during the study period. Over time, the 3-year os slightly improved ($p = 0.051$).

The os for all patients at 3 and 5 years was 34.6% and 25.8% respectively.

Figure 3 presents the os survival curves by treatment modality. Because of small numbers of cases, both primary surgery groups (surgery with or without RT, surgery with CCRT) are combined in this figure. When only patients selected for surgery, RT, and CCRT were included in the analysis, no statistically significant difference in os was observed ($p = 0.28$). The survival of the "no treatment" group is explained by the inclusion of patients with missing data. When controlling for age, sex, and comorbidity, the HR for os among patients selected for CCRT compared with RT alone was 0.871 (95% CI: 0.717 to 1.074; $p = 0.19$; Table III).

Figure 4 presents the Kaplan–Meier os curve for all patients, comparing treatment eras. For the HPC patient population, the addition of chemotherapy to RT was not associated with any statistically significant improvement

TABLE I Demographic and treatment variables for 1333 patients with squamous cell carcinoma of the hypopharynx

Variable	Value	
	(*n*)	(%)
Age group		
35–45 Years	42	3.15
46–55 Years	235	17.63
56–65 Years	514	38.56
66–75 Years	542	40.66
Sex		
Women	245	18.38
Men	1088	81.62
Comorbidities		
0	521	39.08
1	391	29.33
2	191	14.33
3+	230	17.25
Income quintile		
Missing	68	5.1
1 lowest	364	27.31
2	306	22.96
3	223	16.73
4	207	15.53
5 highest	165	12.38
Era		
Before 2000	699	52.44
2000 or later	634	47.56
Sub-site		
1480-Postcricoid	96	7.2
1481-Pyriform sinus	805	60.39
1482-Aryepiglott fold	74	5.55
1483-Post hypopharynx	76	5.7
1488-Hypopharynx NEC	64	4.8
1489-Hypopharynx NOS	218	16.35
Treatment group		
CTx plus RT	14	1.05
No treatment or other	402	30.16
RT with or without Sx	574	43.06
CCRT with or without Sx	154	11.55
Sx with or without RT	175	13.13
Sx plus CCRT	14	1.05

NEC = other specified site; NOS = not otherwise specified; CTx = chemotherapy; RT = radiotherapy; Sx = primary surgery; CCRT = chemoradiotherapy.

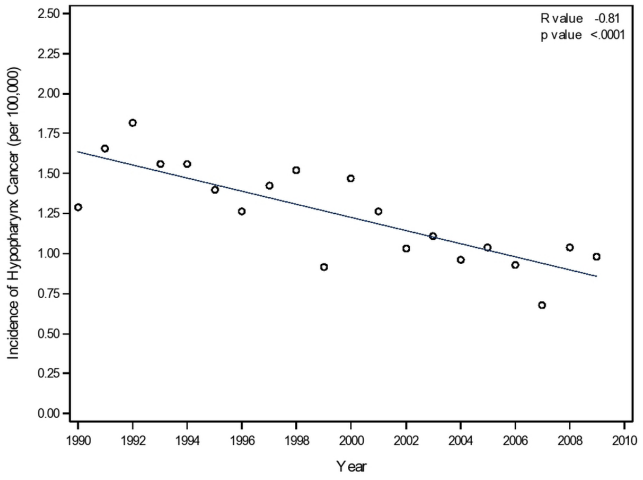

FIGURE 1 The declining incidence (per 100,000 population) of hypopharyngeal squamous cell carcinoma between 1990 and 2010.

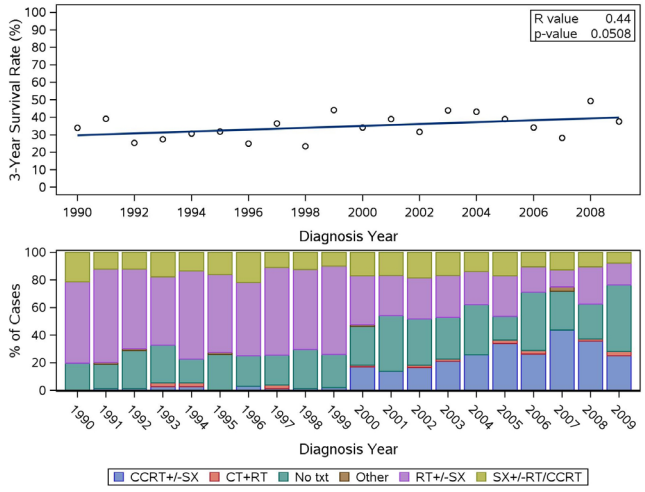

FIGURE 2 The 3-year overall survival (upper panel) and treatment profile (lower panel), by year, for patients with squamous cell carcinoma of the hypopharynx in Ontario. CCRT = chemoradiotherapy; SX = primary surgery; CT = chemotherapy; RT = radiotherapy; No txt = no treatment.

TABLE II Treatment groups by era

Treatment	Era		
	Before 2000	2000 or later	Overall
RT with or without Sx	414	160	574
CCRT with or without Sx	11	143	154
Sx with or without CCRT or RT	102	87	189
CTx plus RT[a]	<10	<10	<15
No treatment	163	234	397
Other[a]	<5	<5	<10
TOTAL	699	634	1333

[a] Small numbers suppressed.
RT = radiotherapy; Sx = primary surgery; CCRT = chemoradiotherapy; CTx = chemotherapy.

in os by log-rank test ($p = 0.145$) or in a multivariable model (HR: 0.917; 95% CI: 0.815 to 1.031; $p = 0.15$).

Figure 5 compares the LFS for patients after 2000 who were selected for CCRT with the LFS for all patients selected for RT alone. No statistically significant difference was observed by log-rank test ($p = 0.44$) or in a multivariable model (HR: 0.903; 95% CI: 0.696 to 1.173; $p = 0.446$).

The LEDFS was 9.93% before 2000 (all patients treated with RT). When LEDFS was compared for patients in the

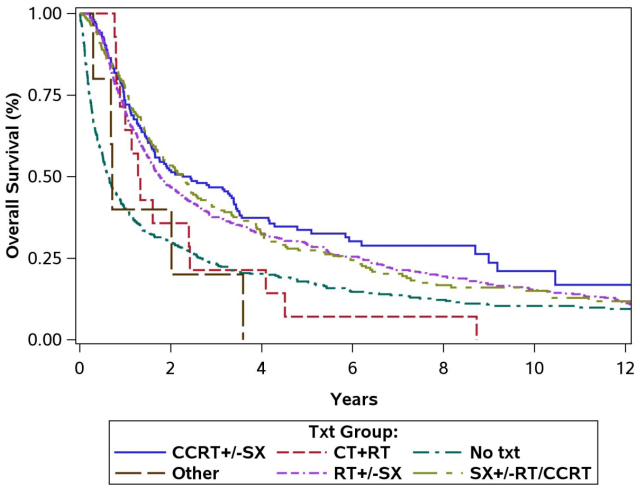

FIGURE 3 Overall survival of all patients with squamous cell carcinoma of the hypopharynx, by treatment. CCRT = chemoradiotherapy; SX = primary surgery; CT = chemotherapy; RT = radiotherapy; No txt = no treatment.

TABLE III Overall survival for patients with squamous cell carcinoma of the hypopharynx treated with surgery or radiotherapy alone compared with chemoradiotherapy

Variable	HR	CI		*p* Value
		Lower	Upper	
Age group				
35–45 Years	0.454	0.284	0.726	0.0010
46–55 Years	0.798	0.651	0.977	0.0289
56–65 Years	Reference			
66–75 Years	1.057	0.902	1.238	0.4913
Sex				
Women	Reference			
Men	1.250	1.038	1.506	0.0184
Treatment				
CCRT with or without Sx	Reference			
RT with or without Sx	0.871	0.707	1.074	0.1957
Sx with or without RT or CCRT	0.958	0.801	1.146	0.6423
Comorbidity				
0	Reference			
1	1.092	0.923	1.292	0.3052
2	1.237	0.995	1.538	0.0553
3+	1.692	1.359	2.107	<0.0001

HR = hazard ratio; CI = confidence interval; CCRT = chemoradiotherapy; Sx = primary surgery; RT = radiotherapy.

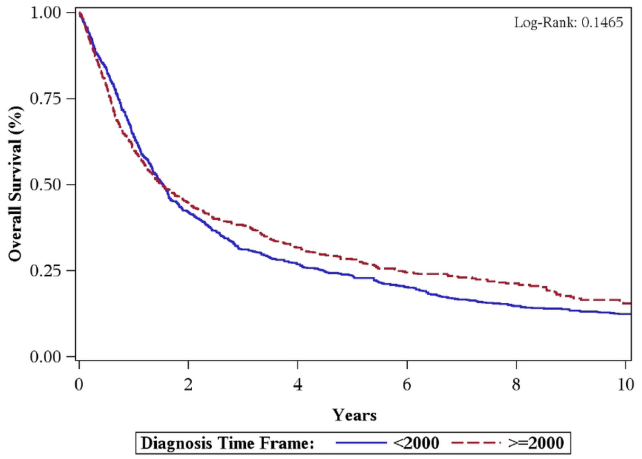

FIGURE 4 Overall survival for all patients with squamous cell carcinoma of the hypopharynx, by treatment era.

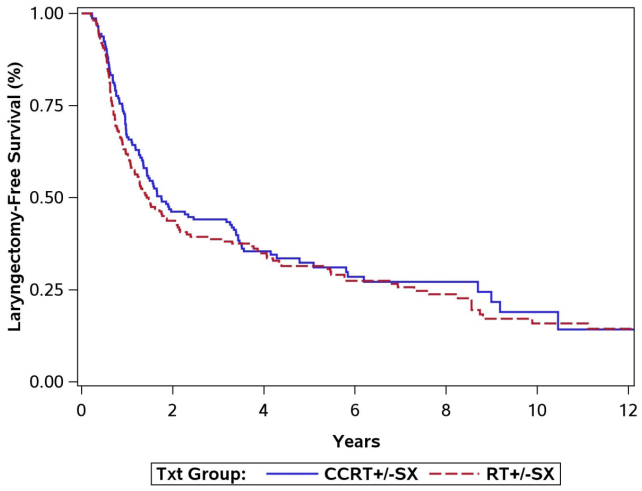

FIGURE 5 Laryngectomy-free survival comparing radiotherapy (RT) alone with chemoradiotherapy (CCRT) for all patients with squamous cell carcinoma of the hypopharynx treated after 2000. Txt = treatment; SX = primary surgery.

post-2000 era who were specifically selected for each treatment, the LEDFS rates were similar (21.25% for RT, 25.87% for CCRT, $p = 0.34$) and had improved from the previous era regardless of treatment.

DISCUSSION

The objective of the present study was to determine the impact of CCRT in the management of HPC, a HPV-negative cancer, at the population level. The 1333 patients identified during 2 decades in Ontario illustrated a declining incidence of HPC and an increasing use of CCRT over time. A marginally statistically significant and progressive slow improvement in 3-year OS was observed, which could have been related to improvements in general medical care or in RT. The variations in the data points by individual year reflect both the small numbers of patients with diverse prognostic factors and treatment selection bias.

Overall, compared with patients treated before the introduction of CCRT, the patients treated after 2000 showed no difference in OS. Moreover, patients selected for CCRT or RT showed no differences in LFS or LEDFS, although patients who received CCRT compared with RT alone almost certainly experienced increased acute and late toxicity[20,21]. What did improve over time was larynx preservation, but such preservation occurred regardless of treatment.

Based on the foregoing findings, physicians, patients, and institutions might want, given the trade-offs of toxicity and of cost to patients and the health care system, to reconsider the role of CCRT in patients with HPC.

Clinical stage would, for many patients, have determined both treatment and outcome, and in the absence of clinical stage data, any interpretation of direct comparisons of treatment effectiveness (RT vs. CCRT) in this patient cohort, including OS (Table III), LFS (Figure 5), and LEDFS is potentially biased as a result of treatment selection, because patients with more extensive disease and thus a worse prognosis could have been treated with CCRT. However, in this patient population, the high rates of significant comorbidity are also a major factor in treatment selection. Furthermore, the treatment selection bias varied over time within and between centres, and patients treated in one centre or in one year with CCRT might have been treated with RT in another year or at another centre. There is also no reason to suspect, nor evidence to support, a theory that the overall spectrum of the disease extent changed, varied, or evolved over the two decades of interest, especially given that HPC is HPV-negative. Treating the same spectrum of patients with a different mix of treatments did not change overall outcomes, despite selection of the best treatment for every patient at the time. Although potentially biased, our findings comparing treatment effectiveness support that observation.

The results of the present study are similar to the site-specific results for HPC within published early clinical trials that compared CCRT with RT alone for all head-and-neck sites. For example, in the trial reported by Adelstein *et al.*[33], the survival of the 16 patients with HPC, comparing RT with CCRT, was reported, and the only survivor was in the CCRT group. In the secondary analyses emerging from a large meta-analysis of studies including multiple sites and heterogeneous treatment protocols, Pignon *et al.*[12] reported a marginal improvement in survival in the CCRT patients compared with those receiving RT alone (1517 pooled cases of HPC). Most recently, based on 2767 HPC cases, Blanchard *et al.*[10] reported that the improvement in OS was only 3.9%.

No randomized trials have compared CCRT with RT alone in HPC specifically; however, single-institution observational studies have been published. Paximadis *et al.*[34] reported on 70 sequential patients, assessing the effectiveness of CCRT as primary treatment (or when added to other regimens) compared with primary surgery or induction CCRT (57 patients received CCRT, 13 received another treatment). Those authors acknowledged that the CCRT group was younger, but the report made no mention of comorbid illness. The authors found that median OS was improved in the CCRT group, reported a 2-year LEDFS of 31.7% for the

CCRT group, and concluded that there was "benefit" with the addition of CCRT for selected patients. Al-Mamgani *et al.*[18] reported on 176 sequential patients treated with either CCRT ($n = 104$) or RT ($n = 74$). Patients with more extensive disease and those who were younger and healthier, with a better performance status, were the ones who received CCRT. The overall OS was 37% (mean follow-up of 34 months), the 3-year OS was 64% for CCRT compared with 36% for RT alone ($p = 0.04$), and the LEDFS was 83% compared with 63% ($p = 0.05$). The authors acknowledged the selection bias, but then concluded that there was a significant improvement in LEDFS, especially in a subset of patients. These two observational studies reported improved survivals of 18%–22%; however, the analyses and interpretations are confounded by treatment selection bias and the failure to account for the effects of comorbidity[32,35], and given those circumstances, their improbable results should be "viewed with skepticism"[36].

The strength of the present study is its design. This is a real-world experience of treating HPC in academic institutions outside of clinical trials. All patients having complete follow-up within the universal health care system in Ontario (legislated data collection and data access at ICES) were included. Selection bias is part of the design because, each year, the academic oncologists at the 8 head-and-neck cancer treatment centres across Ontario selected the best treatment based on the best evidence for each individual patient and his or her cancer. Consistent with the practice guidelines[37] of the day, the same drugs and regimens that were used in the clinical trials that changed practice were used for patient treatment, and therefore knowledge of specific drugs, regimens, and completeness of treatment are not essential to interpret the results. Other strengths include the accuracy of the administrative data, because our results are very similar to those previously reported in a chart-based study that included many of the same and similar patients[9] and because the quality of the OCR data is well known[38].

Limitations of the present study are the selection bias and the missing data in the "no treatment" group—although those limitations apply to treatment comparisons, not era comparisons. In a previous chart-based study of the HPC patient population in Ontario, 17.4% of patients received palliative or no treatment[35]. In the present study, the combination of palliative treatment, no treatment, incomplete treatment data, or no treatment data constituted 28% of the study population, and the difference—approximately 10%—represented the patients with missing data. Because a few of those patients came from all centres in most years and because no patient entries came from a single centre for 2 years, there is no reason to suspect any systematic selection bias in the poor documentation of these 113 patients. The documentation of treated patients with no treatment data is confirmed by the survival curve in Figure 3.

Another limitation is that we cannot report outcomes such as DSS or non-cancer deaths because of the poor reliability of cause-of-death information in the administrative data[38]. The reliability problem can be caused by multiple factors in any disease registry, but HPC specifically is almost certainly problematic given the high incidence of comorbidities and misinterpretations of HPC as metastatic lung disease. It unlikely that an improvement in DSS would be observed with no change in OS, and the results for DSS (data not shown) were consistent with the OS. Similarly, locoregional control or toxicity cannot be reported because site of relapse and specific toxicities were not recorded in the electronic data sources.

CONCLUSIONS

The addition of CCRT to the armamentarium of treatment options for head and neck oncologists in Ontario did not improve OS for patients with HPC. Prognosis for such patients continues to be poor, although the rates of larynx preservation in those who survive have improved. In the absence of specific clinical trial results, and given the increased toxicity of CCRT in otherwise compromised patients with HPC, oncologists, patients, and funders might want to re-evaluate the strength and relevance of the 3.9% improvement seen with the addition of concurrent chemotherapy to RT for HPC.

ACKNOWLEDGMENTS

Ethics approval was granted by the Ethics Review Board of Queen's University (EPID-460-14), and funding was provided by the 2013 Cancer Research Grant Competition, Department of Oncology, Queen's University, Kingston, Ontario. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this paper are those of the author and are independent from the funding sources. No endorsement by ICES or MOHLTC is intended or should be inferred. The project was approved by the ICES Cancer Program. Ms. Susan Rohland was the study coordinator. The data analysis was performed at ICES Queen's by Ms. Rebecca Griffiths.

Parts of this work are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, views, and conclusions reported in the paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

Parts of this work are based on data and information compiled and provided by the Canadian Institute of Health Information (CIHI). The analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of CIHI.

This work was previously presented at a meeting of the Canadian Otolaryngology Society; Winnipeg, Manitoba; 9 June 2015.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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