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ORIGINAL RESEARCH

Treatment Modality and Trends in Survival for Gallbladder Cancer: a Population-Based Study

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Abstract

Purpose There are only a few reports on the treatment-based survival of gallbladder cancer (GBC). The primary objective of this study was to examine the change in treatment modality and the related trends in the survival of GBC.

Methods This study includes all cases of primary GBC diagnosed in the province of Ontario, Canada, from January 2007 to December 2015 with known disease stage. Treatment modalities were classified as *no treatment*, *radiation* or *chemotherapy*, and *surgical resection*. We examined the association between surgical resection and demographics and tumor characteristics and estimated the trends in survival based on treatment modality.

Results In total, 564 patients with GBC were identified, of which 374 (66.3%) were female. Although there were no significant trends in treatment modalities over the study period ($p = 0.276$), survival rates improved for all treatment modalities over time. There was a 35% increase in 5-year survival for the surgical resection group from 2007 to 2015. For patients with stage I–II disease, the 5-year survival rate increased 40% over time. The highest 5-year survival was observed for the surgical resection group in patients with stage I–II disease (0.533 (95% CI, 0.514–0.552)) while the average 5-year survival rate for all patients over the study period was 0.247 (95% CI, 0.228–0.266).

Conclusions Most cases of GBC continue to be diagnosed in the late stage. Five-year survival for the surgical resection group has markedly improved over time, specifically for patients with stage I–II disease which increased from 30% in 2007 to 70% in 2015.

Keywords Gallbladder cancer · Survival analysis · Treatment modality · Trend in survival · Treatment-based survival

Introduction

Gallbladder cancer (GBC) is a rare and understudied neoplasm of the digestive track which is more common in women than in men [1]. GBC is usually diagnosed when the disease is at the late and advanced stage [2]. According to Cancer Research UK, its 1- and 5-year survival rates are reported to be 42.7% and 17.2%, respectively [3]. However, the incidence and mortality rates vary markedly in different countries and ethnicities [4]. For instance, it is a rare cancer in the USA and some European countries, but relatively prevalent in countries such as India, Pakistan, South Korea, and Japan [4]. The presence of gallstones is an important risk factor for GBC [5], although only a small proportion (1–3%) of patients with gallstones develop GBC [6]. Steinert et al. [7] suggested that the introduction of laparoscopic cholecystectomy may have contributed to the earlier incidental diagnosis of GBC and resulted in improvements in overall survival.

Based on an expert consensus [8], surgery is considered to be the only potentially curative treatment for GBC; however,

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this is highly dependent on the stage of the disease. The benefits of surgery are inconclusive in patients with stages II and III disease; patients with stage IV disease are not considered candidates for curative resection [9]. There is a paucity of studies examining the role of adjuvant therapy for GBC. Several studies have indicated higher 5-year survival rates among patients receiving adjuvant chemotherapy [10], but the role of adjuvant radiation therapy is not well-known [11]. In addition, chemotherapy is the preferred treatment modality for only unresectable cases [12].

To our knowledge, only a handful of retrospective population-based studies have reported long-term survival of GBC [11, 13–15]. There is no similar report from Canada or any of its provinces. The province of Ontario is the largest province in Canada with approximately 38.2% of Canada's population [16]. Therefore, the primary objective of this study was to examine the change in treatment modalities and the respective survival rates for GBC in Ontario, while adjusting for relevant demographic and cancer-specific factors such as disease stage and tumor histology.

Materials and Methods

Data Source

This study includes all cases of primary invasive GBC diagnosed in Ontario from January 2007 to December 2015 with known disease stage. Several population-based administrative datasets held at the Institute for Clinical Evaluative Sciences (ICES) were linked to include all cancer patients with their sex, age, date of diagnosis, survival, tumor characteristics, and detailed information on treatment modalities. These datasets include the Ontario Cancer Registry (OCR) (diagnosis date, stage, tumor characteristics), Cancer Activity Level Reporting (chemotherapy and radiation), Discharge Abstracts Database (surgery, radiation, and chemotherapy), National Ambulatory Care Reporting System (chemotherapy and radiation), Ontario Health Insurance Plan claims (chemotherapy and radiation), Same Day Surgery datasets (chemotherapy and radiation), and Registered Person Database (age, sex, and date of death). The datasets were linked using unique encoded identifiers provided by ICES.

Patients were identified based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, for primary invasive GBC with the codes C23.9 in the OCR dataset. Patients were included if they were 18 years or older at the time of diagnosis. Age at diagnosis was classified as < 60, 60–69, 70–79, and 80 and over. Patients that were diagnosed solely based on death certificate or autopsy were excluded because their survival is not known.

Treatment modalities were classified as follows: (1) *no treatment* if we could not find any records of radiation, chemotherapy, or surgical resection in the datasets; (2) *radiation* or *chemotherapy* (RT/CT) for patients that received radiation or chemotherapy but had no record of surgical resection; and (3) the *surgical resection* for patients that received surgical resection with or without radiation or chemotherapy. The following factors were considered to determine treatment classification. First, a preliminary literature review indicated that surgery is being considered the only curative treatment [8]. Second, there were small frequencies in some groups which necessitated merging some groups together; for example, there were only 17 patients who received only radiation and 8 patients who received resection and radiation (see Supplementary Table 1). For each patient, a treatment modality was accounted for and included in the analysis only if it was received up to 1 year after diagnosis.

Staging data has been made available in Ontario since 2007. The Cancer Care Ontario uses a "best stage" grouping approach where stage is assigned to each case based on pathologic TNM when available and clinical TNM otherwise [17]. It collects stage data using the staging criteria of the American Joint Committee on Cancer or the Collaborative Stage initiative. If a case has more than one valid stage value, the "best stage" is derived based on a pre-specified algorithm if a collaborative stage is available; otherwise, in case of availability, the stage group provided by the treating regional cancer center is used [18]. Stages I and II were combined into one group (stage I–II) because of small sample sizes. This analysis only includes patients with known cancer stage. Tumor histology was classified as adenocarcinoma (AC) or other.

Statistical Analysis

First, descriptive statistics were reported for demographics and tumor characteristics based on treatment modality (Table 1). Second, we conducted an analysis to examine the relationship between demographics (sex and age groups) and tumor characteristics (stage and histology) and the likelihood of undergoing surgical resection. For this analysis, treatment modalities were regrouped as surgery versus no surgery (reference group) and the effect of each variable was reported as odds ratio (OR) with 95% confidence interval (95% CI). Third, we estimated the survival rate for patients diagnosed with GBC from 2007 to 2015 with follow-up until the end of 2016. We used a flexible parametric (Royston-Parmar) model to estimate survival rates [19, 20]. This model provides smooth estimates of survival using restricted cubic splines on the log cumulative excess hazard scale. This approach adopts a piecewise approach which makes it more flexible compared with other traditional methods in imitating the actual trends in survival pattern [21]. We fitted a model by incorporating age group, sex, year of diagnosis, histology of

Table 1 Distribution (*N* (%)) of demographics and tumor characteristics at diagnosis based on treatment modality among GBC patients

	No treatment	Radiation/ Chemotherapy	Resection	Total
Age group				
< 60	8 (6.9)	42 (36.2)	66 (56.9)	116
60–69	30 (18.9)	55 (34.6)	74 (46.5)	159
70–79	48 (24.4)	54 (27.4)	95 (48.2)	197
≥ 80	45 (48.9)	21 (22.8)	26 (28.3)	92
Age, mean (SD)	74.4 (9.6)	66.9 (11.1)	66.6 (11.1)	68.5 (11.2)
Sex				
Male	34 (17.9)	66 (34.7)	90 (47.4)	190
Female	97 (25.9)	106 (28.3)	171 (45.7)	374
Histology				
Adenocarcinoma	81 (21.2)	109 (28.5)	192 (50.3)	382
Other	50 (27.5)	63 (34.6)	69 (37.9)	182
Stage				
I–II	43 (18.9)	26 (11.4)	159 (69.7)	228
III	16 (18.6)	26 (30.2)	44 (51.2)	86
IV	72 (28.8)	120 (48.0)	58 (23.2)	250
Year				
2007–2009	57 (23.3)	77 (31.4)	111 (45.3)	245
2010–2012	46 (24.9)	54 (29.2)	85 (45.9)	185
2013–2015	28 (20.9)	41 (30.6)	65 (48.5)	134
Total	131 (23.2)	172 (30.5)	261 (46.3)	564

tumor, stage of tumor, treatment modality, and the interaction term between each two variables into a multiple statistical model using a forward approach. The likelihood ratio test was used to compare different models to reach to a final model. All variables included in the final model were statistically significant ($p \leq 0.05$). Then, based on the final model, trends in 1- and 2- and 5-year survival rates for each treatment modality and stage of disease were estimated while adjusting for other variables. The local institutional ethics board reviewed and approved the research proposal for this retrospective study.

The flexible parametric model was fitted using the freely available stpm2 program [19] for the Stata package. All the statistical analyses were conducted using the Stata/MP 15.1 (Stata Corporation, College Station, TX).

Results

In total, 564 patients were identified with primary invasive GBC, of which 374 (66.3%) were female. The mean age at diagnosis was 68.5 with a standard deviation (SD) of 11.2 years. The mean age at diagnosis was not significantly different between male (67.8 (SD = 11.4)) and female (68.9 (SD = 11.2)) patients ($p = 0.256$). Table 1 presents patients' age group, sex, and tumor characteristics based on treatment modality. Overall, there was no significant difference in receiving surgical resection between male (47.4%) and female (45.7%) patients ($p = 0.711$). The older the patient was, the lower was the chance of receiving a surgical resection. For instance, 56.9% of patients < 60 years received surgical resection compared with 28.3% of patients 80 and over. Approximately 70% of patients with stage I–II disease received surgical resection, compared with 23.2% of patients with stage IV disease. In addition, the rate of no treatment among stages I–II was 18.9%, which increased to 28.8% for stage IV disease. In contrast, only 11.4% of patients with stage I–II disease received radiation or chemotherapy, but this increased to 48.0% for patients with stage IV disease. Although there were no specific changes or trends in the three specified treatment modality groups over the study period ($p = 0.276$), there was a slight decrease in the proportion of adjuvant chemotherapy from 2007 to 2015 (slope = 0.022, p for trend = 0.0184). In addition, we observed a significant decrease in stages I–II disease in contrast with stages III–IV disease (slope = −0.0201, p for trend = 0.0160). However, survival rates improved for all treatment modalities over time.

Factors Related to Surgical Resection

Table 2 presents the predictors of surgical resection including sex, age group, year of diagnosis, histology, and stage of disease. There was no significant difference based on sex (OR 0.95; 95% CI, 0.64–1.43). Although the odds of receiving

Table 2 Predictors of surgical resection in GBC patients

Variable	OR(95% CI)
Sex	
Male	Reference group
Female	0.95 (0.64, 1.43)
Age group	
< 60 years	Reference group
60–69 years	0.67 (0.39, 1.16)
70–79 years	0.71 (0.42, 1.19)
≥ 80 years	0.24 (0.13, 0.47) $^{++}$
Year of diagnosis	1.05 (0.97, 1.13)
Histology	
AC[1]	Reference group
Other	0.63 (0.42, 0.95) $^{+}$
Stage	
I–II	Reference group
III	0.42 (0.25, 0.72) $^{+}$
IV	0.12 (0.08, 0.18) $^{++}$

$^{+}p < 0.05$, $^{++}p < 0.001$, [1] Adenocarcinoma

surgical resection decreased with age, it was not statistically significant for patients 60–69 and 70–79 compared with < 60 years. However, it was highly significant for patients 80 and over (OR 0.24; 95% CI, 0.13–0.47), which indicates that the chance of surgical resection for patients 80 and over was 76% less compared with patients < 60 years. The odds ratio of surgical resection for a patient with tumor histology other than adenocarcinoma was 0.63 (95% CI, 0.42–0.95) compared with a patient with adenocarcinoma.

Trends in Survival Based on Treatment Modality and Stage

The final model for survival analysis included treatment modality, age group, disease stage, and year of diagnosis. Treatment modality and year of diagnosis were also included as time-dependent variables. Neither histology of tumor nor any of the interaction terms were shown to be statistically significant predictors for survival and were excluded from the final model. The adjusted survival curves for treatment modalities are shown in Fig. 1. Survival was best for the surgical resection group. Interestingly, the survival for the radiation or chemotherapy (RT/CT) group was higher than the survival for the no-treatment group for up to 1.5 years after diagnosis, but the effects wore off after 1.5 years. Trends in 1-, 2-, and 5-year survival rates from 2007 to 2015 based on treatment modality are depicted in Fig. 2. Although the survival increased over time for all treatment modalities (including the *no-treatment* group), it was more pronounced for the surgical resection group. Again, the RT/CT group had better survival up to 1 year, but this effect wore off over time so that the no-treatment group had a higher 5-year survival compared with the RT/CT group. Most improvements were observed in the 5-year survival rate for patients who underwent surgical resection, where survival rate increased more than 35% from 2007 to 2015.

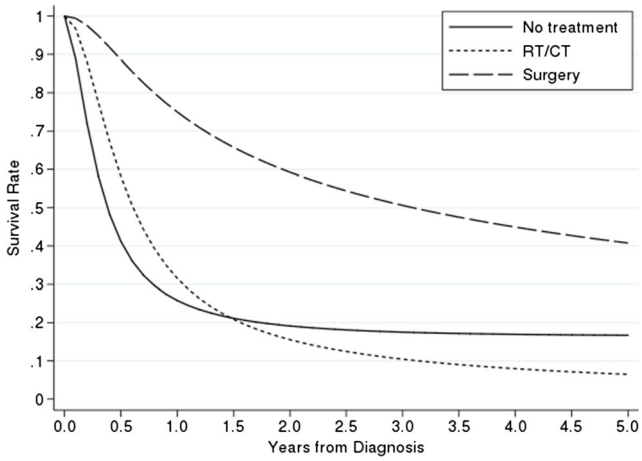

Fig. 1 Adjusted survival curves based on treatment modality

Trends in survival based on disease stage are shown in Fig. 3, where stages I and II were combined into one group due to small sample sizes. Although the survival rate increased over time for all stages, the largest increase was for patients with stage I–II disease, where the 5-year survival rate increased from 30% in 2007 to 70% in 2015.

Overall 5-Year Survival Rate

The average model-based 5-year survival rates over the study period based on disease stage and treatment modality are presented in Table 3. The highest 5-year survival was observed for the surgical resection group in patients with stage I–II disease (0.533 (95% CI, 0.514–0.552)), followed by stage I–II disease and no treatment (0.366 (95% CI, 0.323–0.410)). The lowest survival rates were observed for patients with stage IV disease in the RT/CT group (0.031 (95% CI, 0.025–0.038)) and no-treatment group (0.049 (95% CI, 0.037–0.061)). The average 5-year survival rate for all patients over the study period was 0.247 (95% CI, 0.228–0.266).

Discussion

This is the first population-based study in Canada providing insight into the trends in treatment and adjusted treatment-based survival for GBC after controlling for patient- and disease-specific factors. There was no major change in treatment modalities over the study period from 2007 to 2015. The only change observed was a slight decrease in the use of adjuvant chemotherapy (slope = 0.022, p for trend = 0.0184).

Although the survival rate improved for all treatment modalities over time, this was much more evident for the surgical resection group. The reported survival rates vary between different studies and in different countries. On average, we found a 25% 5-year survival rate, which is higher than the 20% reported by Justo et al. [22] in a much smaller sample, and also higher than 17.2% as reported by Cancer Research UK [3]. In this study, the survival of stage I–II disease continuously improved over the study period. Overall, 69.7% of patients with stage I–II disease underwent surgical resection, but this proportion dropped to 51.2% for stage III and to 23.2% for stage IV disease. Although surgery is the only curative treatment [8], its role in stage III disease is not clear [9]. In the absence of evidence from prospective randomized trials, resection of the gallbladder, adjacent liver, and regional lymph node dissection is the recommended operative approach for resectable GBC [23]. As per the National Comprehensive Cancer Network (NCCN) guidelines, patients with resectable disease undergo surgery, followed by adjuvant chemotherapy [11]. In patients with unresectable disease, chemotherapy is

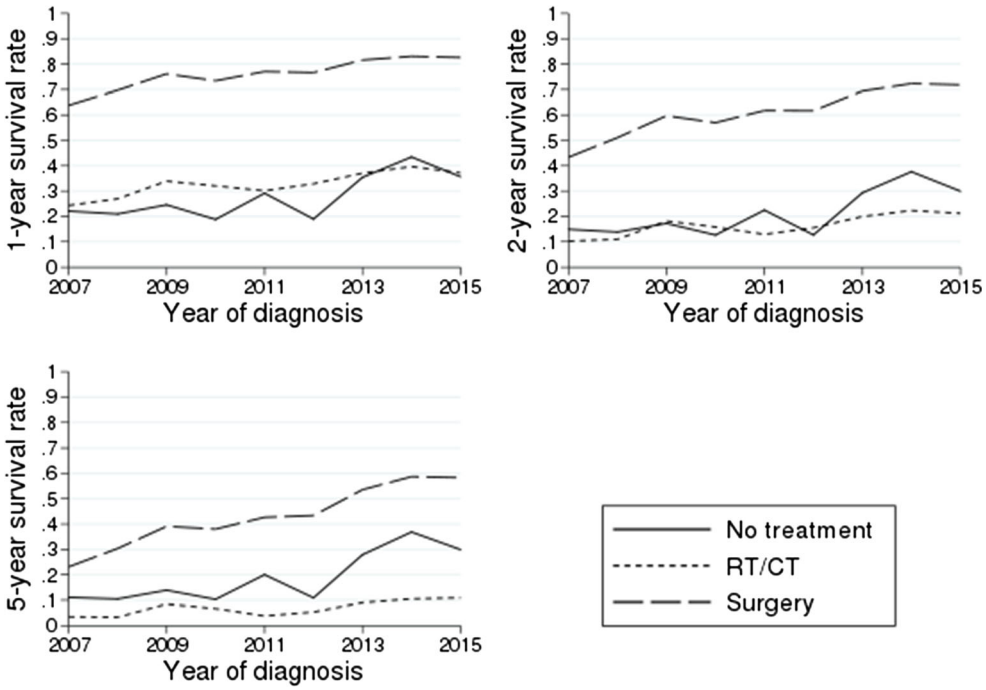

Fig. 2 Trends in 1-, 2-, and 5-year survival based on treatment modality

the main modality of treatment [12, 24]. In our study, 60% of GBC cases were diagnosed at stages III and IV. The poor survival among patients with GBC has traditionally been attributed to high rates of stage III and IV disease at the time of diagnosis, which is presumably due to the anatomic position of the gallbladder and non-specificity of symptoms [25]. However, after the introduction of laparoscopic cholecystectomy, the overall number of cholecystectomies performed has increased. This could have resulted in an earlier incidental diagnosis of GBC, in turn improving the overall survival rate over time [7, 11]. In contrast, this study observed an increase in stage III and IV disease. It has also been hypothesized that improvements in survival are partly due to aggressive radical surgery and improved surgical techniques [26].

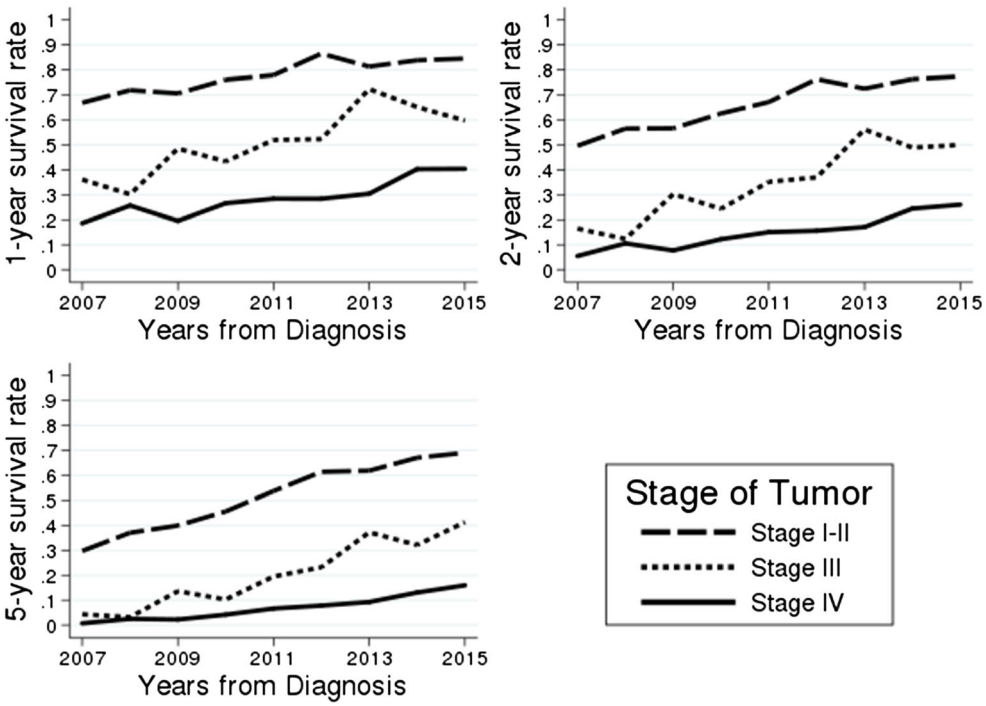

Fig. 3 Trends in 1-, 2-, and 5-year survival based on stage of the disease

Table 3 Five-year survival rate (SR) based on stage and treatment modality

Stage	No treatment		Radiation or chemotherapy		Surgical resection		Total	
	n	SR (95% CI)	*n*	SR (95% CI)	*n*	SR (95% CI)	*n*	SR (95% CI)
Stage I–II	43	0.366 (0.323, 0.410)	26	0.225 (0.186, 0.264)	159	0.533 (0.514, 0.552)	228	0.467 (0.445, 0.488)
Stage III	16	0.163 (0.110, 0.215)	26	0.059 (0.038, 0.080)	44	0.329 (0.292, 0.365)	86	0.216 (0.183, 0.250)
Stage IV	72	0.049 (0.037, .061)	120	0.031 (0.025, 0.038)	58	0.123 (0.093, .152)	250	0.058 (0.048, 0.067)
Total	131	0.167 (0.137, 0.197)	172	0.065 (0.051, 0.078)	261	0.408 (0.382, 0.433)	564	0.247 (0.228, 0.266)

This study did not have enough number of patients undergoing adjuvant radiation or chemotherapy to assess their separate effects on the survival of patients with GBC (Supplementary Table 1). This remains to be evaluated in studies with larger sample sizes. In general, there are only a few retrospective reports on the effects of adjuvant radiation or chemotherapy on GBC. However, there are some reports indicating improvements in survival for patients undergoing adjuvant chemotherapy [10]. A recent systematic review and meta-analysis also reported beneficial effects of adjuvant radiotherapy on the survival of GBC patients [27]. Of the total 564 patients in our study, the majority of those that did not undergo surgical resection received either no treatment ($n = 131$) or chemotherapy alone ($n = 123$). Due to the small number of patients undergoing radiation alone ($n = 17$), or chemoradiation ($n = 32$), we were unable to disentangle the effects of radiation, chemotherapy, and chemoradiation. However, given the comparable larger sample size of chemotherapy alone, if any form of palliative therapy was effective in increasing the survival of the RT/CT group, we suspect it must have been chemotherapy, rather than radiation alone or chemoradiation. Combinations of palliative chemotherapy are currently being used for patients with unresectable or metastatic GBC [28–30].

This retrospective study has several limitations. First, there was an incomplete submission of cancer staging data for patients diagnosed with GBC, which limited our ability to analyze the entire cohort between 2007 and 2015. Second, the use of administrative datasets limited the ability to capture various other factors that may have been involved in the treatment decision-making process (e.g., patient preference). Third, the analysis of a heterogeneous administrative cohort stratified over a 9-year period could have imposed an inherent bias into the findings. This study also has several strengths. It includes a population-based dataset with detailed information on patient and cancer characteristics. We quantified the effect size for factors associated with treatment modality using a logistic regression and investigated the trends in survival rates over a 9-year period based on treatment modality while adjusting for important tumor characteristics such as stage. We used a flexible parametric model for survival analysis which is much more advanced and flexible than the standard parametric models or Cox regression in mimicking the actual trends in mortality and survival pattern [21].

Conclusions

Overall, there was no major change in the treatment modalities over the study period from 2007 to 2015, except for a slight decrease in adjuvant chemotherapy. The majority of cases with GBC continue to be diagnosed in later stages, with poor short-term prognoses. Survival for patients with stage I–II disease has improved over the study period and their five-year survival rate increased 40% between 2007 and 2015. Our findings indicate that if any form of palliative therapy was effective in increasing the survival of the RT/CT group, it must have been chemotherapy, rather than radiation only or chemoradiation.

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Compliance with Ethical Standards

The local institutional ethics board reviewed and approved the research proposal for this retrospective study.

Conflict of Interest The authors declare that they have no conflicts of interest.

Disclaimer The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed in the material are those of the authors and not necessarily those of CIHI. Also, parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The

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