Gallbladder cancer, a vanishing disease?

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Abstract

Objective  Gallbladder cancer (GBC) is a rare gastrointestinal malignancy. A retrospective population-based study was conducted to evaluate trends in incidence, treatment, and outcome of GBC in the latter three decades in the south of the Netherlands.

Methods  All patients diagnosed with GBC diagnosed in the Dutch Eindhoven Cancer Registry area between 1975 and 2008 were included (n = 659). Trend analyses were conducted for treatment and survival.

Results  During this time period, standardized incidence in females and males plummeted from 4.5 to 0.7 and from 2.0 to 0.4 per 100,000 inhabitants, respectively. Resection rates decreased from 74.3 to 53.4 %. Chemotherapy and radiotherapy rates did not change and were used sparingly. Five-year survival remained stable (10 %) over time.

Conclusion  The age-standardized incidence of GBC declined drastically over the last three decades. An increasing number of early cholecystectomies for gallstones may play a role. Parallel to the decreasing incidence of stomach cancer, the effective treatment of Helicobacter pylori may also have resulted in a lowered incidence of GBC.

Keywords  Gallbladder cancer · Incidence · Treatment · Survival

Introduction

Gallbladder cancer (GBC) is a rare gastrointestinal malignancy, but it is the most common cancer of the biliary tract. In addition to age-, race-, and gender-related differences, there are also geographic factors determining incidence of GBC. For instance, it is relatively common in Chile, Japan, and northern India [1, 2]. Trends in incidence may vary substantially over time. Declining rates were reported in Sweden, Denmark, and France [3] although incidences remained stable in Italy [3]. In Europe, GBC accounts for approximately 33,000 new cases and 24,000 new deaths yearly [4]. The incidence of GBC in the Netherlands was 0.5 per 100,000 persons in 2008 (males 0.4 per 100,000 inhabitants, females 0.6) [5].

GBC is very aggressive cancer type with a median survival of 3–11 months and a 3–13 % 5-year survival [6]. The late appearance of clinical symptoms is one of the main determinants as life expectancy is determined by clinical stage at the time of detection [7]. More than half of all GBCs is not resectable at the time of diagnosis [6].

Accurate statistics on GBC occurrence and outcome are essential for planning and evaluation of control programs as well as for purpose of research into causes, treatment, and prevention. Aim of the present study is to investigate long-term trends in incidence, stage of disease at presentation, treatment, and survival among patients diagnosed with GBC in the southern part of the Netherlands between 1975 and 2008.
Methods

The Eindhoven Cancer Registry collects data since 1975 on all cancer patients in a large part of the southern Netherlands comprising some 2.3 million inhabitants. This population-based registry owes its existence to the joint efforts of six pathology departments, ten community hospitals, and two radiotherapy institutions. Information on demographic specifics, diagnosis, stage of GBC, treatment, and follow-up was obtained from the medical records by specially trained administrators of the cancer registry using standard extraction techniques. Registration routinely occurred between 6 and 18 months after the diagnosis. By means of an independent case certification, the trustworthiness of this registration is reported to exceed 95% [8].

Analyses

Incidence rates are calculated as the number of new patients per 100,000 inhabitants per year. Trends are age-standardized as suggested by the European Standardized Rate (ESR) [9]. Tumors were registered according to the International Classification of Diseases for Oncology. Survival data obtained during three consecutive time periods were compared: the period between 1975 and 1990, between 1991 and 2000, and between 2001 and 2008. The first period was chosen because tumor node metastasis (TNM) staging for GBC was not utilized before 1990. The remaining 18-year period was divided into two even 9-year intervals. The revised TNM classification system as suggested by the International Union against Cancer was used for staging [10]. Staging occurred on the basis of depth of tumor infiltration, number of nodes, and presence of distant metastases. Trends in proportional stage distribution are shown as the proportional distribution of the TNM stage in the respective period. Stages that were used for these calculations were usually obtained “postoperatively.” If unknown, the preoperative stage was used. Surgery and other therapy (chemotherapy and/or radiotherapy) are also shown per period.

All analyses were performed using SAS/STAT statistical software (SAS system 9.1.3, SAS Institute, Cary, NC). Since cause-of-death was not available at an individual patient level, survival was calculated using all-cause mortality. Kaplan–Meier survival curves were calculated for all patients. Difference in 5-year crude overall survival was tested using the log-rank test. The follow-up was complete for patients diagnosed up to 1 January 2010. Missing data for patients in the database were treated as unknown during statistical analysis. All tests were two-sided. p values <0.05 were considered statistically significant.

Results

Some 659 cases of GBC were diagnosed during the 33-year observation period. Female–male ratio was 2.8:1 (485 women and 174 men). Median age at the time of diagnosis was 72 years (range 27–89 years). The age-standardized incidence decreased dramatically. For females, the incidence decreased more than sixfold from 4.5 to 0.7 patients per 100,000 inhabitants. Among males, the decrease was some fivefold (2.0–0.4) (Fig. 1). Table 1 shows the proportional stage distribution at diagnosis. Figure 2 shows the age-standardized incidence of patients with GBC in the southern part of the Netherlands compared to patients with GBC in the Netherlands from 1989 to 2009.

Of the 659 patients, 65% (n = 425) underwent surgery (Table 2). However, the number of surgical cases decreased from 74% in 1975–1990 to 53% in 2001–2008. Other treatment options were used sparingly. Radiotherapy was administered to 33 (5%) patients, whereas systemic
Chemotherapy was received by just 3% [21] patients. Percentage of patients receiving any treatment was stable over time. The overall median survival was 6 months with a 10% 5-year overall survival (Fig. 3). Figure 4 shows the survival of patients that were operated compared to nonoperated. Median survival was 8 and 5 months, respectively. A 5-year overall survival of 14% was found in patients that were operated, whereas there was no single survivor in the nonoperated group.

**Table 2** Treatment of patients with gallbladder cancer in the south of the Netherlands, according to period of diagnosis

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<tbody>
<tr>
<td>Surgery</td>
<td>225 (74.3%)</td>
<td>125 (57.9%)</td>
<td>75 (53.4%)</td>
<td>425 (64.5%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>14 (4.6%)</td>
<td>2 (0.9%)</td>
<td>5 (3.6%)</td>
<td>21 (3.2%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>21 (6.9%)</td>
<td>10 (4.6%)</td>
<td>2 (1.4%)</td>
<td>33 (5.0%)</td>
</tr>
<tr>
<td>No treatment</td>
<td>43 (14.2%)</td>
<td>79 (36.6%)</td>
<td>58 (41.4%)</td>
<td>180 (27.3%)</td>
</tr>
</tbody>
</table>

Numbers within brackets indicate the percentages of patients who underwent the respective treatment.

The global, European, and Dutch GBC incidence rates per 100,000 persons in 2008 were 2.0, 1.9, and 1.5, respectively [11]. Overall, Dutch data are prospectively available since 1989. However, the Eindhoven Cancer Registry accommodating some 2.3 million Dutch inhabitants is already accumulating data from 1975 on. Trend analysis demonstrates a five- to sixfold decline in GBC incidence in
both females and males. Data from our National Registry also show a (smaller) decline, but data collection only covers the last two decades [5]. Moreover, Hoogendoorn reported a decline of admissions for gallbladder cancer [12]. Similar overall declining incidence rates were also reported in the US [13], New Mexico [14], Sweden, Denmark, and France (Bas-Rhin) [3] as also worldwide [15]. In contrast, an increase in incidence has been noted in Chile [15] and Asia [3]. These dissimilar trends suggest that geography plays a major role in the diagnosis.

One factor that is postulated to enhance the risk of GBC is a history of gallstones or gallbladder disease [16]. An inverse relationship between cholecystectomy rates (facilitated by the advent of ultrasonography in the late 1970s [17] and the introduction of laparoscopic techniques in the 90s [18]) and number of GBCs is suggested by others [19, 20]. Our national Center of Statistics has calculated that the number of cholecystectomies has indeed increased by 40 % from 1995 to 2007 (10.9 vs 15 per 10,000 inhabitants) [21]. These calculations underscore the beneficial effects of (early) removal of the gallbladder on the lifetime risk on GBC.

The exact pathophysiology of GBC is multifactorial. However, the endemic (prolonged) presence of toxic bacteria may play a role in its development. For instance, a significantly higher frequency of helicobacter species is found in GBC patients [22, 23]. Interestingly, a steady decrease in the number and severity of Helicobacter pylori infections has been shown in the south of the Netherlands [24]. Remarkably, effective treatment strategies for H. Pylori have also resulted in declining incidences of stomach cancer [25–27]. It may well be that Helicobacter species colonize the hepatobiliary tract causing some persistent low-grade biliary tract infection. These events may ultimately lead to chronic inflammation and gallstone formation, especially due to urease production [28, 29]. The presence of gallstones may further aggravate chronic inflammation and can induce transformation that is further amplified by various toxins and carcinogenic metabolites produced by the Helicobacters [30, 31]. Early removal of gallbladders by a relatively noninvasive surgical technique may reduce exposure to these toxic products and may lower the risk on GBC.

The present study found decreased rates of surgery for GBC over the last three decades. It is argued that the advancements in imaging have resulted in proper selection of cases eligible for surgical exploration [13, 32, 33]. Surgery poses the only cure as chemotherapy and radiotherapy have proved largely ineffective in the past although recent reports have suggested some promising results using gemcitabine and cisplatin in patients with advanced or metastatic GBC. Molecularly targeted agents are under development [34, 35]. Due to the rarity of the tumor, most studies are phase II clinical trials with a small number of patients. Chemotherapy and radiotherapy were incidentally used in the time frame of present study.

Survival after GBC is notoriously poor. The present study also showed a stable 10 % overall 5-year survival rate over the last three decades. Some series report similar 5-year overall survival rates (0–12 %) [36, 37] although others showed better results varying from 21 to 38 % [32, 33, 38, 39]. Survival in surgical patients was 3 months longer compared to patients receiving conservative therapy. However, the group of surgical patients is probably heterogeneous as it also incorporates unforeseen removal of small cancers. The fact that operated patients have a longer survival could be the result of selection bias. The present report does not allow for an in-depth analysis as details of the exact operative procedures were not available in the early years of our registry.

Conclusion

The age-adjusted incidence of gall bladder cancer (GBC) in the south of the Netherlands has decreased dramatically over the last three decades. This fortunate trend is possibly associated with the larger number of cholecystectomies as well as with the effective treatment modalities for Helicobacter pylori infections. Recent advances in imaging modalities have reduced the number of patients eligible for surgery. Survival remained stable over time.

References

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