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Geographic Variation in T2 Gallbladder Carcinoma Survival: Data on 316 Patients

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Geographic Variation in T2 Gallbladder Carcinoma Survival: Data on 316 Patients

By

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Bachelor of Arts
Williams College
2010

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An abstract of
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Abstract

Geographic Variation in T2 Gallbladder Carcinoma Survival: Data on 316 Patients

By Mia Susan DeSimone

Background: The reported prognosis of gallbladder carcinoma (GBC) varies widely worldwide due, at least in part, to the differences in staging. To assess differences in prognosis independent of disease stage, this study examines survival in a geographically diverse sample of cases with pathologically confirmed T2 GBC, defined as primary tumor that invades into perimuscular connective tissue without extension beyond the serosa or into the liver.

Methods: Data on patient demographic characteristics and survival were obtained from 316 cases of histologically proven T2 GBC from collaborating institutions in three countries and were microscopically verified: Chile (n=137), South Korea (n=105), and the USA (n=74). Overall and disease-specific survival estimates were compared across the three sites using multivariable Cox proportional hazard models, which controlled for patient age and sex.

Results: Compared to patients from South Korea, patients from Chile had a significantly worse prognosis with respect to overall and, in particular, disease-specific survival. The corresponding differences between South Korea and the USA were also pronounced and statistically significant. Patient age and sex were not associated with prognosis in either analysis.

Conclusions: There are notable geographic differences in GBC survival even after limiting the comparisons to patients with confirmed T2 stage. Thus, an important next step is to compare clinical practices in different countries.

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Mia DeSimone

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CHAPTER 1:
INTRODUCTION

Gallbladder carcinoma (GBC) is an aggressive and often fatal cancer with considerable geographic variability in prognosis (1-8). By comparing survival with tumor- and patient-related characteristics in a geographically diverse sample of cases with pathologically confirmed T2 GBC, we can discern the possible contributions of stage and other factors to the geographic variability in GBC survival.

Background

Historically, GBC has been universally fatal with a five-year post-diagnosis survival of less than 5% (9). Over time, with earlier diagnosis and advances in surgical treatment, diagnostic techniques, and perioperative care, five-year survival has reached 21-69% after curative resection (1, 2, 4, 9-19). Yet many cases of GBC are still discovered at invasive stages with limited treatment options and poor prognosis (1, 2, 4, 9-19).

Tumor stage and type of surgical intervention are important prognostic factors: five-year survival reaches 100% for T1 disease after simple cholecystectomy, ranges from 70-90% for T2 disease with *en bloc* resection, and decreases to 30-50% for T3 disease and 0-32% for T4 disease, even after radical surgery (1, 2, 4, 9-19). Patient factors such as female sex and advanced age are also associated with more invasive disease and worse prognosis (1, 5, 7, 9, 20-22). Due to the relatively aggressive nature of GBC, much of the current preventative strategies involve behavioral interventions to curb overweight and obesity and prompt diagnosis and surgical treatment of gallstones, another major risk factor for GBC (5).

GBC demonstrates pronounced geographic variations in incidence, mortality, and survival (4-8). Latin America and Asia represent two major high-risk geographic regions, with Chile and Japan particularly affected (3, 5, 6, 23-25). These geographic variations are often

attributed to disparities in prevalence of GBC risk factors, imaging methods, disease awareness, diagnostic and management practices, access to care, and stage at diagnosis, although the exact reasons for the observed patterns of disease occurrence still remain unclear (3, 5, 6, 26). In fact, recent literature even suggests that geographic disparities in survival exist within the same GBC stage (3, 6, 16). The current study would be the first large, international, multicenter cohort study to specifically examine the geographic variations reported in survival within a single GBC tumor stage in order to elucidate some of the factors contributing to these disparities.

Statement of the Problem

The geographic variation in GBC survival has prompted this investigation into the tumor- and patient-related characteristics that may be influencing prognosis. There are numerous explanations presented in the literature to account for the observed geographic variation, ranging from differences in epidemiologic-genetic-causative factors to healthcare access, diagnosis, and management practices. However, this study offers the first international, multicenter cohort study that specifically examines and compares survival of patients from three countries diagnosed with pathologically proven GBC within a specific GBC tumor stage. By controlling the tumor stage, we eliminate the survival differences attributable to variation in stage at diagnosis. Taking into account disease stage will allow a more comprehensive evaluation of geographic differences in GBC survival.

Purpose of the Study

This study aims to elucidate the geographic variations in survival within a single GBC tumor stage by comparing overall and disease-specific survival in a large, international, multicenter cohort of patients diagnosed with pathologically confirmed T2 GBC from three countries: Chile, South Korea, and the USA.

Research Questions

1. Is there a significant geographic difference in survival within an international cohort of patients from Chile, South Korea, and the USA with pathologically confirmed T2 GBC?

2. Are geography, patient age, and/or patient sex associated with survival within an international cohort of patients from Chile, South Korea, and the USA with pathologically confirmed T2 GBC?

Significance Statement

Through better understanding the reasons for geographic variation in prognosis of T2 GBC, we can begin to move toward the development of internationally accepted, practical, and relevant diagnostic criteria for GBC.

Research Design

Pathologic cholecystectomy slides and data were obtained from 316 cases of histologically proven T2 GBC from eight collaborating institutions. Microscopic pathology slides of cholecystectomy specimens were carefully classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging criteria for GBC, and only cases that demonstrated convincing perimuscular invasion with no extension beyond the serosa or into the liver were included (27). Overall and disease-specific survival estimates were calculated and compared across three geographic areas: Chile, South Korea, and the USA. Multivariable Cox proportional hazard analysis was performed to further examine the association between geographic location and survival after adjusting for sex and age at diagnosis.

CHAPTER 2:
REVIEW OF THE LITERATURE

Carcinoma of the Gallbladder

Although the most common and aggressive malignancy of the extrahepatic biliary tract, gallbladder carcinoma (GBC) is a relatively rare neoplasm with a poor prognosis (1-4, 28). Earlier diagnosis can improve prognosis, yet due to the vague, nonspecific, insidious presenting symptoms similar to those associated with gallstones, the anatomic position of the gallbladder, and the aggressive nature of GBC, the disease is rarely discovered at a resectable stage (1, 3, 4, 29, 30). Therefore, patients with GBC can have a dismal five-year survival even with surgical intervention and medical treatment and often palliation is the only feasible option (1, 17, 28, 31, 32). While recent advances in surgical techniques improved survival, GBC remains an aggressive disease with high metastatic potential due to its close anatomic proximity to lymphovasculature (1, 13).

Now in the laparoscopic era, over half of all GBC cases are detected incidentally at an early, resectable, possibly curable stage upon examination of a cholecystectomy specimen for suspected benign disease (14, 16, 21, 30, 33-37). These occult cancers tend to be early and asymptomatic, whereas symptomatic GBC typically present once invasive, thus carrying a very poor prognosis (34, 38). At the time of diagnosis, most of these neoplasms have already invaded adjacent structures, most commonly the liver, cystic duct, bile ducts, and portal-hepatic lymph nodes, and may have even seeded the peritoneum, gastrointestinal tract, and lungs (13). Furthermore, inadequate processing and grossing of the specimen often hinders accurate pathologic evaluation and staging of GBC (33).

Risk Factors

Causing irritative trauma and chronic inflammation, gallstones and infectious agents, like *Helicobacter bilis, Helicobacter pylori, Salmonella typhi* and *Salmonella paratyphi*, serve as important risk factors for GBC (3, 5, 30). The duration of biliary calculus disease is positively associated with GBC risk (39). Obesity and multiparity are also common risk factors (5, 40). Thus, the main preventative measures include diagnosis of gallstones with resultant cholecystectomy and behavioral interventions to address overweight and obesity (5). Although Japan reports high rates of GBC, there is a lower incidence of obesity and gallstone-associated GBC among Japanese patients (3, 39). In fact, in a recent study of Japanese patients with GBC, less than half were associated with gallstones while 50% had no discernible risk factors (23). This study, along with others, suggests existence of a significant carcinogenic pathway that is unrelated to biliary calculus disease (3, 23).

Gallbladder Cancer Worldwide

While GBC is overall relatively rare throughout the world, there is considerable geographic variability with certain populations reporting significantly higher incidence rates compared to others (3-6, 23, 24, 33, 41-43). In general, GBC is less common in Australia, New Zealand, North America, and Northern Europe, particularly among persons of European descent (below 3 per 100,000/year in women and 1.5 per 100,000/year in men) compared to Central and Eastern Europe, South America (particularly Bolivia, Chile, and Ecuador), some areas of India, Japan, Korea, and Pakistan, and among Native Americans and Mexican-Americans (up to 27 per 100,000/year) (1, 4, 5, 7, 20, 41). In a recent comprehensive review of the global epidemiology and burden of GBC across 45 countries, Randi and colleagues (6) confirmed that GBC survival continues to not only vary significantly by stage but also by geographic area. GBC incidence

rates were highest in Ecuador, India, Japan, Korea, Pakistan, and some countries in Central and Eastern Europe (5, 6). Latin America and Asia represent two major high-risk regions, with Chile and Japan particularly affected (3, 5, 6, 23, 24). Japan reports one of the highest incidences of GBC accounting for 3.5% of cancer deaths in women and 1.25% in men (25). In addition, GBC is endemic in Chile, when compared to the rates in American centers, and the fourth leading cause of cancer-related death among Chilean women (44). Furthermore, a significantly larger proportion of GBC in Chile is discovered incidentally, possibly signifying a difference in prevalence, diagnostic protocol, preoperative imaging, and access to care (34).

Worldwide, the increased use and accessibility of laparoscopic cholecystectomy has contributed to an increase in the proportion of patients diagnosed with GBC incidentally (45). However, this pattern has not been observed in Japan, where the rate of incidental GBC is far lower and the rate of preoperative diagnoses is much higher than in North America and Northern Europe (3, 23). Differences in pathogenesis support these regional differences but have not resulted in significantly different clinical behaviors (3). The ethnic, racial, and sex variations in incidence rates throughout the world have been attributed to disparities in prevalence of GBC risk factors in different populations, although the exact reasons for the observed patterns of disease occurrence still remain unclear (3, 5, 6, 26). The geographic variability in incidence of GBC could also be influenced by differences in imaging practices or disparities in disease awareness and diagnostic and management practices (3).

Pathology and Staging of Gallbladder Cancer

The vast majority of GBC tumors are adenocarcinomas (21). There are a number of staging systems for GBC across the world, including the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC), Nevin's staging system, and the

Japanese Biliary Surgical Society staging system (1, 28, 46, 47). Most widely accepted, the AJCC/TNM staging system defines the degree of invasion of the primary tumor (T-stage), whether the cancer has spread to regional lymph nodes (N-stage), and if the cancer has spread to other organs (M-stage). This staging system categorizes GBC into the following tumor stages: carcinoma in situ (Tis), tumor invades the lamina propria (T1a), tumor invades the muscular layer (T1b), tumor invades the perimuscular connective tissue without extension beyond the serosa or into the liver (T2), tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure (T3), and tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures (T4) (27, 33).

Tumor stage, as classified by the AJCC/TNM staging system, is the strongest overall predictor of patient survival and reflects worsening prognosis with increasing stage (1, 34, 47-50). However, the unique histologic features of the gallbladder—abundant undulations in the epithelium, lack of muscularis mucosa, irregular and porous muscularis, extensive invaginations into the muscularis and often deeper—make it difficult to classify early invasive carcinoma and differentiate high-grade dysplasia/carcinoma-in-situ (Tis) from early invasion into lamina propria (T1a) or into muscularis (T1b) (33). As a result, pathologists in high-risk regions, like Asia, Chile, and India, have decided to instead refer to Tis/T1a/T1b cases as “early GB cancer” (33). This new staging concept has been proven to be clinically relevant and justified: compared to advanced GBC, the long-term survival of early GBC nears 90% in 10 years and the prognosis is not significantly different between Tis, T1a, and T1b cases (33, 51-55). While pathologists still assign a tumor stage according to the AJCC/TNM staging protocol for GBC, the “early” versus

"advanced" staging concept is increasingly utilized for accurate prognostic classification and appropriate stratification for management (56).

In early 2014, a consensus meeting of expert panelists sponsored by the American Hepato-Pancreato-Biliary Association (AHPBA) established practice guidelines after reviewing the latest evidence on the management of GBC (2). Considering the historic under-sampling of gallbladder specimens that leads to under-diagnosis and under-staging, these experts called for more unity in approaches to the initial pathologic evaluation, classification, and staging of GBC (2). Especially within high incidence areas where GBC is a significant contributor to mortality, like Chile, India, and Japan, the pathologic assessment of routine gallbladder specimens should include the microscopic assessment of a minimum of three random sections and the cystic duct margin (2). Dysplastic or neoplastic specimens warrant even more extensive sampling (2). Hari and colleagues (57) have also called for more accurate nodal staging in addition to tumor staging in order to improve prognostic evaluation. In addition, contrasted cross-sectional imaging and diagnostic laparoscopy is the minimum staging evaluation recommended for patients with suspected or proven GBC (2). Collaboration among international institutions and disciplines will be crucial to ensure the development of more internationally accepted, practical, and relevant diagnostic criteria for GBC (33).

Management of Gallbladder Cancer

Management of GBC often involves resection surgery as a staging modality and therapeutic strategy (2). Surgical management of a gallbladder mass should only be considered once the provider has ruled out distant metastases, unresectable regional nodal disease, and/or local invasion into critical structures (2, 30).

Surgical Treatment

Surgical removal of the entire tumor is the single most curative treatment for localized GBC (1, 30, 58). Due to the vital structures in close proximity to the gallbladder, complete surgical and potentially curative resection with achievement of a negative margin is a challenge (1, 13). Consequently, it is estimated that only 25% of patients will undergo this potentially curative surgery, and the recommended surgical management varies globally (2, 3). The extent of surgical resection, from simple cholecystectomy to include partial hepatectomy with or without regional lymph node dissection, varies based on staging and invasion of neighboring anatomic structures (1, 2, 20, 30). Controversy exists as to the appropriate extent of liver resection and lymph node dissection as well as the relative advantage of excision of the common bile duct, major hepatectomy, major vascular resection, and resection of adjacent organs (3, 12, 30, 58).

Simple cholecystectomy has typically been performed to treat patients with T1 GBC as long as the resection margins are negative (12, 13, 16, 29, 37, 47, 59-65). These patients require close follow-up to monitor for local recurrence (13). Compared to lesions confined to the mucosa, T2 lesions have a greater risk of spread to the regional lymph nodes and unsuspected invasion into the adjacent organs (14). According to a recent expert consensus statement, patients with early GBC (T1b-2) should receive an *en bloc* resection of adjacent liver parenchyma in addition to a radical cholecystectomy (2). Based on abundant evidence from the literature, the necessary surgical treatment to improve survival outcomes for T2 disease is radical cholecystectomy with wedge resection of the gallbladder bed and regional lymph node dissection to achieve margin-negative resection for cure (1, 12-14, 16, 19, 29, 35, 37, 38, 50, 54, 64, 66-72). Because the majority of T2 lesions are discovered incidentally during or after simple

cholecystectomy, these patients frequently require re-resection of the gallbladder fossa with extended regional lymphadenectomy (14, 37, 50, 64, 66, 73).

In the past, the surgical management of T2 GBC has been controversial in North America because of limited data (38). Since then, not only has the European and Japanese literature demonstrated improvements in survival with the use of radical resection over cholecystectomy alone, there have been several studies that prove simple cholecystectomy to be inadequate to treat T2 disease (38). After cholecystectomy alone, residual cancer, which can often be fatal for the patient, is discovered 35-40% of the time and as high as 74% in a retrospective analysis at a single institution (12, 21, 74). Miller and Jarnagin (20) observed that a simple cholecystectomy among patients with T2 disease resulted in a five-year survival of only 20-40%. Another large study found that when compared to patients with T2 disease who underwent simple cholecystectomy, patients who underwent radical resection had an almost threefold increase in median survival (75). Similarly, de Aretxabala and colleagues (64) and Fong and colleagues (14) demonstrated that five-year survival for T2 GBC increased from 20% and 19%, respectively, after simple cholecystectomy to 70% and 61%, respectively, after radical resection. Furthermore, combining an *en bloc* resection with cholecystectomy increased the five-year survival to 80-90% (20, 76). Even though the morbidity and mortality of the procedure are relatively low, ranging from 5-54% and 0-21%, respectively, they are not insignificant (14, 38, 77, 78).

Although the rate of lymph node metastases in T2 disease ranges from 19-44%, there is limited evidence to determine the ideal extent of regional lymph node dissection; many agree that regional lymph node dissection is effective for positive nodes (1, 9, 16, 50, 54, 66, 77). Several studies concluded that radical resection of T2 disease should only be performed in the absence of regional lymph node metastasis (12, 66, 71). Patients with lymph node metastasis,

perineural invasion, or both should be offered additional treatment after radical resection to bolster the prognosis (66). Tumor with infiltrative types also warrants aggressive surgical management (19). An expert consensus statement recommended that an adequate lymphadenectomy for staging purposes should include intraoperative assessment of any suspicious regional nodes, evaluation of aortocaval nodal basin, and retrieval of at least six nodes (2). Patients with T1b, T2, or T3 incidental GBC should undergo radical second resection with a goal of a margin-negative resection for cure after contraindications, like advanced disease and poor performance status, have been considered (2, 14, 37, 50, 54, 64). As the survival and resectability rates for T3 and T4 GBC are low, these patients should only be offered radical surgery in expert, multidisciplinary centers after careful consideration of the risks and benefits (2, 10, 79).

Laparoscopic Treatment

Laparoscopic treatment for GBC has been contraindicated in the past because of fear of tumor cell dissemination during surgery and belief in its inadequacy for radical surgery (80-84). The laparoscopic approach remains contraindicated when GBC is suspected preoperatively (4, 14). While there have been several studies on the safety and effectiveness of a laparoscopic approach for other gastrointestinal malignancies, there have been few reports that examine the long-term survival outcomes and oncologic safety of laparoscopic cholecystectomy in patients with GBC (80, 85, 86). In their 10-year prospective cohort study of patients with GBC who received laparoscopic cholecystectomy, Yoon and colleagues (80) found that patients with T1 disease had a five-year survival of 100% and patients with T2 disease had a five-year survival of over 90%, and recurrence was rare. Compared to survival from open surgery, these outcomes were at least similar or better (87).

In the past, survival after surgery for early GBC was more varied, ranging from 45-100% for T1a, 36.5-100% for T1b, and 43-93% for T2 (80, 82, 88, 89). These variations can possibly be attributed to differences between institutions and their patient populations or to the survival analyses conducted using extrapolation and with limited follow-up (80, 82, 88, 89). The favorable long-term oncologic results reported by Yoon and colleagues (80) supported the use of laparoscopy for the treatment of patients with early GBC without invasion of the liver. In addition, there is evidence to support continuing the laparoscopic approach when GBC is discovered incidentally during the procedure (45). More recently, several other studies have confirmed that laparoscopy does not cause worse outcomes than the open technique when the stage-adjusted therapy is offered (20, 36, 58, 86, 88, 90, 91). However, despite the evidence, the uncertainty persists (36).

Medical Treatment

Systemic medical therapy for GBC is used in curative and palliative settings either alone or in combination with radiation and surgical resection (1, 2). Adjuvant systemic chemotherapy and/or chemoradiation should be considered in patients with preoperatively staged T3-4 disease with local lymph node involvement, patients with resected GBC with positive margins, patients with T2 and persistent local lymph node involvement following resection for cure, and patients with unresectable locally advanced disease with distant lymph node spread (2, 30). Biliary drainage can be offered to patients with unresectable or metastatic GBC and jaundice to improve quality of life (30).

Surveillance

As there is no data to support aggressive surveillance after surgical resection of GBC, it is up to the discretion of the physician to determine an appropriate schedule (30). Benson and

colleagues (30) of the National Comprehensive Cancer Network (NCCN) Hepatobiliary Cancers Guidelines Panel recommended that patients who undergo extended cholecystectomy for GBC receive imaging studies every six months for two years, with reevaluation if the initial disease progresses.

Adherence to Guidelines

Although the national consensus guidelines for the management of localized T2 GBC recommend radical cholecystectomy, Wright and colleagues (74) investigated adherence and determined that widespread practice patterns in the USA are not consistent with these recommendations. They proposed several explanations for the discrepancy in observed and expected survival for T2 GBC (74). First, they suggested that the indications for major resection might not be widely appreciated, preventing patients from receiving referral for the appropriate surgical management (74). Second, there may not have been widespread adoption of the more aggressive management strategy because surgeons may not fully appreciate the importance of tumor staging as a management and prognostic indicator (12, 74). Finally, surgeons may be hesitant to perform an aggressive re-resection in an older patient population with more medical comorbidities that could complicate the procedure (74).

Gallbladder Cancer Prognosis

Generally, a diagnosis of GBC confers a poor prognosis because it tends to be discovered at an invasive, often noncurative stage (1, 2, 13, 14, 17-19). In fact, the majority of patients diagnosed at a curative stage have been detected incidentally upon pathologic examination of a cholecystectomy specimen (14, 16, 37). Inflammation of the gallbladder wall that distorts the architecture in addition to a higher proportion of flat, unapparent lesions explains the difficulty in detecting early small lesions on imaging or macroscopic examination (16). In the past, GBC had

a reported overall five-year survival of less than 5% (1, 28, 31, 32). Over time, with more advances in surgical treatment, diagnostic techniques, and perioperative care, there have been some improvements in long-term survival and morbidity and a greater possibility of a cure (2, 4, 9-14). Now, five-year overall survival ranges from 21-69% after curative resection (1, 2, 4, 9-19). Yet despite these advances, GBC continues to be frequently discovered at invasive stages with limited treatment options and poor prognosis (1, 2, 4, 9-19). In fact, the majority of cases, approximately 70% according to a recent series, are unresectable at diagnosis (10, 42, 92). Thus, as reported in India, Japan, Mexico, and the USA, the main determinant of survival globally is stage at diagnosis (22, 23, 93, 94).

Prognostic Factors

In a recent study, Hari and colleagues (57) described several independent predictors of disease-specific survival, including age, T1 subtype, tumor grade, tumor histology, radiation, and surgery type. The same study also reported that independent predictors of overall survival were age, T1 subtype, tumor grade, tumor histology, race, and surgical procedure (57). It is well documented in the literature that primary tumor, lymph node metastasis, and TNM stage are the most significant prognostic factors influencing survival after surgical resection of GBC (16, 47, 63, 66, 78, 95, 96). In patients with advanced GBC, adjuvant chemotherapy, tumor differentiation, hepatic invasion, and surgical margin status are other prognostic factors that must be considered (50, 97).

Patient factors such as female sex and advanced age are associated with more invasive disease and worse prognosis (1, 5, 7, 9, 20-22). Patient age is a predictive factor of disease-specific survival; the younger the age at treatment, the better the predicted survival (57). In

contrast, upon clinical exam, jaundice and a palpable mass indicate advanced disease and both confer a worse prognosis (1).

Tumor stage of the TNM staging system, or the depth of penetration, is one of the most critical prognostic factors as well as management indicators for GBC (1, 2, 4, 9-19, 37, 47, 50, 74, 77, 98, 99). Patients with T1 tumors, ones that do not invade beyond the lamina propria or muscle layer, have a favorable five-year survival of nearly 100% and a relatively low risk of nodal metastasis (1, 2, 4, 9-19, 66, 87, 100, 101). For T2 tumors, the overall five-year survival is intermediate from 70-90% depending on whether *en bloc* resection was performed, the risk of nodal involvement ranges from 33%-60%, and the proportion of distant metastases is 16% (1, 2, 4, 9-19, 61, 66, 77, 101, 102). Tumors that perforate the serosa or invade the adjacent organs confer a dismal prognosis: the overall five-year survival is 30-50% for T3 disease and 0-32% for T4 disease (1, 2, 4, 9-19). In T4 disease, the risk of nodal involvement increases to 69-79% and the proportion of distant metastases increases to 79% (1, 2, 4, 9-19, 66, 79, 101, 102). Likely discovered at an earlier stage, incidental GBC is associated with a better prognosis than when compared with patients with a preoperative suspicion for GBC (34).

The extent of nodal or hepatic involvement is also an important prognostic feature (1, 12, 14, 16, 18, 63, 66, 99). In particular, nodal status is the most significant determinant of outcomes in patients with T1 GBC (12, 54, 75). For example, patients with T1 disease with negative nodes have a nearly 100% five-year survival compared with patients with T2 disease and positive nodes who demonstrate a strikingly decreased survival (12, 16, 37). Metastases to regional lymph nodes appear to be an early sign of invasive GBC, occurring before involvement of the liver or other adjacent organs (50). Residual tumor status is another important independent

prognostic factor, influencing surgeons to always strive to achieve negative resection margins for GBC (37, 50, 63, 66).

Compared to more advanced stages, the prognosis of T2 GBC is intermediate with improved long-term survival after radical resection (50, 64, 66). The reported prognosis of T2 GBC varies widely based on surgical management (66). The five-year survival of patients with T2 ranges from 10-40% after simple cholecystectomy and 37-95% after radical resection (12, 31, 37, 47, 66, 71, 74, 77, 80, 101, 103-105). Prognosis of T2 GBC also varies across continents (3). When evaluating differences in disease presentation, surgical treatment, and survival among GBC patients in Chile, Japan, and the USA, Butte and colleagues (3) discovered that tumor extent (tumor stage and lymph node and bile duct involvement) was a more significant predictor of survival than country of origin. In fact, there were notable disparities in disease extent among the three centers, resulting in differences in types of surgical treatment and rates of curative resection (3). However, among patients who received a curative intent resection, survival was very similar across the three sites (3). The median disease-specific survival in T2 patients treated in the USA was 18.9 months compared with 19 months in Japan and 13.2 months in Chile (3). Similar differences were seen when comparing five-year disease-specific survival: 20% in Chile and 30% in both Japan and the USA (3). The five-year disease-specific survival among patients treated with curative intent was much improved: 40% in Japan, 45% in the USA, and 60% in Chile (3). These findings suggest that the geographic variations seen in GBC survival may be explained by differences in access to appropriate surgical treatment and curative resection (3).

Prevention, Screening, and Future Directions

One of the key prevention strategies for GBC involves diagnosing and removing gallstones because they are associated with carcinogenesis (1, 106). However, even given this

association, the evidence to support performing a prophylactic cholecystectomy in an asymptomatic patient remains inadequate (1). Offering a prophylactic cholecystectomy should be considered in patients in the high-risk category: gallstones greater than 2-3 centimeters in diameter, associated polyps, nonfunctioning gallbladder, porcelain gallbladder, pancreaticobiliary reflux, segmental adenomyomatosis, and xanthogranulomatous cholecystitis (1, 106, 107). In addition, patients who undergo a gastrectomy may suffer from delayed gastric emptying, placing them at higher risk of gallstones and gallbladder cancers, and, therefore, should be offered a concomitant cholecystectomy (1, 107). Due to the often delayed diagnosis at an unresectable stage, future research calls for improvements in early, accurate diagnosis and safe, successful management strategies (1).

Conclusion

GBC is an aggressive malignancy that demonstrates considerable geographic variability in incidence, mortality, and survival worldwide (1-8). In order to reduce the disease burden, the scientific community recommends addressing key modifiable risk factors (overweight, obesity, and duration of biliary calculus disease) and ensuring access to care, early diagnosis, appropriate surgical management, and adequate perioperative care (1, 2, 4, 5, 7, 9-22). Some attribute the geographic variation in long-term survival from GBC to disparities in prevalence of GBC risk factors, imaging methods, disease awareness, diagnostic and management practices, access to care, and stage at diagnosis, yet the exact reasons for the observed patterns of disease occurrence still remain unclear (3, 5, 6, 26). Although tumor stage is one of the most critical prognostic factors as well as management indicators for GBC, recent literature suggests that geographic disparities in survival exist even within the same GBC stage (1-4, 6, 9-19, 37, 47, 50, 74, 77, 98, 99). This pattern suggests that there is a complex interplay between the various prognostic

factors across countries. Therefore, further research is necessary to closely examine the geographic variations reported in survival within a single GBC tumor stage between different countries to elucidate some of the factors contributing to these disparities.

CHAPTER 3:
MANUSCRIPT

GEOGRAPHIC VARIATION IN T2 GALLBLADDER CARCINOMA SURVIVAL: DATA ON 316 PATIENTS

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Contribution of the Student

For this manuscript, the student participated in all aspects of the project, from study design and development to statistical analysis and manuscript preparation with guidance and editorial assistance from Drs. Michael Goodman and N. Volkan Adsay.

ABSTRACT

Background: The reported prognosis of gallbladder carcinoma (GBC) varies widely worldwide due, at least in part, to the differences in staging. To assess differences in prognosis independent of disease stage, this study examines survival in a geographically diverse sample of cases with pathologically confirmed T2 GBC, defined as primary tumor that invades into the perimuscular connective tissue without extension beyond the serosa or into the liver.

Methods: Data on patient demographic characteristics and survival were obtained from 316 cases of histologically proven T2 GBC from collaborating institutions in three countries and were microscopically verified: Chile (n=137), South Korea (n=105), and the USA (n=74). Overall and disease-specific survival estimates were compared across the three sites using multivariable Cox proportional hazard models, which controlled for patient age and sex.

Results: Compared to patients from South Korea, patients from Chile had a significantly worse prognosis with respect to overall and, in particular, disease-specific survival. The corresponding differences between South Korea and the USA were also pronounced and statistically significant. Patient age and sex were not associated with prognosis in either analysis.

Conclusions: There are notable geographic differences in GBC survival even after limiting the comparisons to patients with confirmed T2 stage. Thus, an important next step is to compare clinical practices in different countries.

INTRODUCTION

Gallbladder carcinoma (GBC), the most common malignancy of the extrahepatic biliary tract, is an aggressive and often fatal disease (1-5). Incidence rates of GBC demonstrate pronounced geographic, ethnic, racial, and cultural variations (4, 6-9). In general, GBC is rare in Australia, Canada, New Zealand, Northern Europe, and the USA (below 3 per 100,000/year in women and 1.5 per 100,000/year in men) and is more common in Central and Eastern Europe, South America (particularly Bolivia, Chile, and Ecuador), and some areas of India, Japan, Korea, and Pakistan with reported rates up to 27 per 100,000/year (1, 4, 6, 7, 10, 11).

There is also considerable geographic variability in GBC mortality (3, 4, 6, 9, 10, 12-17). For example, Chile reports the highest incidence and mortality rates of GBC worldwide, and GBC is the fourth leading cause of cancer-related death among Chilean women (18). In comparison, the disease contributes relatively few deaths to cancer mortality in North America and Northern Europe (1, 4, 6). The ethnic, racial, and gender variations in incidence and mortality rates across geographic regions have been attributed to disparities in prevalence of GBC risk factors, although the exact reasons for the observed patterns still remain unclear (3, 6, 9, 19).

In addition to geographic differences in GBC incidence and mortality, survival among patients diagnosed with GBC also differs by country (1, 3, 9, 11, 14, 20-36). While some of these differences in disease prognosis may be explained by differences in stage at diagnosis, recent literature suggests that geographic disparities in survival exist even within the same GBC stage (3, 9, 37). Some have attributed this intra-stage variation in survival to differences in prevalence, diagnostic tendencies, imaging practices, and access to care, although the pattern does not appear to be consistent across countries (3, 13, 38).

A better understanding of the relative contributions of stage at diagnosis compared to other factors may require an international, multicenter cohort study that would specifically examine the geographic variations in survival within a single GBC tumor stage. With these considerations in mind, the purpose of this study was to compare the overall and disease-specific survival in a cohort of patients diagnosed with pathologically confirmed T2 GBC from three countries: Chile, South Korea, and the USA.

METHODS

Study Population

The analysis dataset included 316 cases of GBC from eight collaborating institutions in the three countries. All cases were verified to be stage T2 during an international consensus meeting that re-analyzed and reassessed the criteria defining T2. Information on patient demographic characteristics (sex, age at diagnosis, and country of residence), diagnosis date, follow-up duration, and vital status at follow-up was obtained from the medical records. Vital status was defined using the following categories: alive, dead of GBC, dead of secondary disease related to GBC (e.g., peritoneal carcinomatosis), dead of another disease, and dead of unknown reason. Vital status information was available through January 2017. The diagnosis dates ranged from 1987 to 2015.

Pathology Data Collection

Microscopic pathology slides of cholecystectomy specimens were reviewed for convincing perimuscular invasion with no extension to the serosa or into the liver (pT2). The majority of cases were reviewed by pathologists from each participating country, and all cases were reviewed by pathologists from at least two countries. The extent of invasion for each GBC

case was then classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for GBC (39). Cases representing carcinoma in situ (pTis) that extended to the Rokitansky-Aschoff sinuses were excluded. Cases of tumor that invaded into the lamina propria or muscularis without growth into the perimuscular fibrous tissue (pT1) were also excluded. Finally, cases demonstrating involvement of the serosal and/or hepatic surface (pT3) were omitted. All of the cases from each of the three countries were processed in a tertiary setting with adequate sampling (microscopic evaluation of a minimum of five sections per case) performed in each cohort. On average, seven sections per case were available for examination, and almost all of the cases from Chile and South Korea were totally submitted for microscopic examination.

Data Analysis

Kaplan-Meier curves and the corresponding log-rank tests were used to compare survival across the three countries. Multivariable Cox proportional hazard analysis was performed to further examine the association between geographic location and survival after adjusting for sex and age at diagnosis (≤60 years, 61-70 years, and >70 years). Results of these multivariable models were expressed as adjusted hazard ratios (HRs) and reported along with the corresponding 95% confidence intervals (CIs) and p-values. The multivariable survival analyses were conducted for both all-cause and GBC-specific mortality. For GBC-specific mortality, the event of interest was defined as death from GBC or from secondary disease related to GBC. All models were tested for proportional hazard assumptions by inspecting the log-log curves. Two-way interactions were tested by including cross-products for site with each of the remaining covariates. The standard statistical software package SPSS (version 23 for Windows; IBM Corp.,

Armonk, NY) was used to analyze the data. The cutoff for statistical significance was set at the two-sided alpha error of 0.05.

RESULTS

As shown in Table 1, slightly less than half (43%) of study participants were from Chile, one-third (33%) from South Korea, and the remaining 23% from the USA. Women represented the majority of study participants (73%); however, the proportions of women differed by site (87% in Chile, 56% in South Korea, and 70% in the USA). The study sample was equally distributed across age categories, and this age distribution was generally similar across the three countries.

The overall survival varied significantly by geographic site, with South Korea consistently demonstrating the highest survival across the entire follow-up period (Figure 1). At one year of follow-up, the survival differences were particularly pronounced between South Korea and Chile (85% and 70%, respectively) whereas survival in the USA was 80%. By three years of follow-up, the difference between Chile and the USA was no longer evident (50% and 55%, respectively), but overall survival was significantly higher (70%) in South Korea. The five-year overall survival remained similar between Chile and the USA (45% and 35%, respectively), but was still significantly higher in South Korea (55%).

The differences in disease-specific survival were generally similar to those seen with overall survival (Figure 2). At one year of follow-up, disease-specific survival was virtually equivalent in South Korea and the USA (90% and 85%, respectively), whereas survival in Chile was only 70%. By three years of follow-up, the differences between disease-specific survival in Chile, South Korea, and the USA were more pronounced: South Korea had the highest survival

(75%), followed by the USA (65%), and then Chile (55%). As the follow-up duration lengthened to five years after diagnosis, the disease-specific survival curves in Chile and the USA converged at 50%, which was significantly lower than survival in South Korea (70%).

Results of the Cox proportional hazards analyses of all-cause and GBC-specific mortality are presented in Tables 2 and 3. No significant interactions were present. After controlling for age and sex, patients from South Korea had significantly lower mortality compared with their counterparts in the other two sites with adjusted HR (95% CI, p-value) estimates of 1.75 (1.12-2.75, p=0.015) for the USA and 1.89 (1.27-2.83, p=0.002) for Chile. The observed difference further increased in the analyses of GBC-specific mortality with adjusted HR (95% CI, p-values) of 1.94 (1.14-3.31, p=0.015) and 2.41 (1.51-3.84, p<0.001) for the USA and Chile (relative to South Korea), respectively. After controlling for study site, age at diagnosis and patients' sex were not related to survival in any of the analyses.

DISCUSSION

The results of this large, international, multicenter cohort study demonstrate that T2 GBC patients from South Korea had a significantly better prognosis than T2 GBC patients from Chile and the USA. Previously, it had been speculated that the higher survival reported in South Korea could be explained by differences in the criteria used to determine invasiveness, leading to over-staging of carcinoma in situ (pTis) that extends to the Rokitansky-Aschoff sinuses and mimics pT2 GBC. However, in this study, pathologists from each participating country reviewed the majority of cases, and pathologists from at least two countries reviewed all cases. The stage of the tumors was confirmed at an international consensus meeting (in April 2016). Additionally, pathologic sampling phenomenon is also unlikely to be a factor because all of the cases from

each of the three countries were processed in a tertiary setting with adequate sampling (microscopic evaluation of a minimum of five sections per case) performed in each cohort. For all cases combined, the mean number of slides examined per case was seven. In fact, in Chile and South Korea, almost all of the cases were totally submitted for microscopic examination. Therefore, geographic differences in pathologic diagnostic criteria and sampling adequacy were unlikely to bias this study. The difference in survival is more likely attributable to different healthcare practices (e.g., post-operative management) or regional differences in prognostic risk factors and the pathogenesis of GBC (3, 6, 9, 13, 19).

Several earlier studies have examined geographic variations in GBC survival by comparing various features of the disease across regions of the world (4, 6-9, 19). In a recent comprehensive review of the global epidemiology and burden of GBC among 45 countries, Randi and colleagues (9) confirmed that GBC survival continues to not only vary significantly by stage but also by geographic area. In comparison, when evaluating differences in disease presentation, surgical treatment, and survival among GBC patients in Chile, Japan, and the USA, Butte and colleagues (3) discovered that tumor extent (tumor stage and lymph node and bile duct involvement) was a more significant predictor of survival than country of origin. In fact, there were notable disparities in disease extent among the three centers, resulting in differences in types of surgical treatment and rates of curative resection (3). However, among patients who received a curative intent resection, survival was very similar across the three sites, suggesting that the geographic variations seen in GBC survival may be explained by differences in access to appropriate surgical treatment and curative resection (3).

The geographic variation in survival is often attributed to disparities in stage at diagnosis; however, in our study, the differences in survival persisted after the data were restricted to T2

disease. It is possible that some of the geographic variation in GBC survival is attributable to the different prevalence of certain prognostic factors, such as duration of biliary calculus disease and mutations in regulatory genes *K-ras* and *TP53*, although it is unlikely these factors completely explain the results observed in this study (3, 6, 9, 19). Furthermore, preliminary studies indicate that GBC arising in pancreaticobiliary maljunction, which is attributed to reflux of pancreatic enzymes to the gallbladder, may represent a different biologic pathway in cancer formation.

One potential explanation is the different levels of T2; however, our preliminary results indicate that there are no significant differences between these cohorts in terms of the different levels of T2 substage cases they contain. Although recent literature has evaluated the association between survival, disease presentation, and surgical treatment of GBC among institutions in different countries, the present study is the first international, multicenter collaboration to specifically examine the geographic variations in survival within a single GBC tumor stage that is carefully characterized and adequately sampled (3, 9).

Several studies have demonstrated sex- and age-related differences in survival (1, 3, 6, 7, 9, 11, 40-42). Because gallstones and duration of biliary calculus disease are major risk factors for GBC, women and the elderly are at high risk of developing GBC (1, 3, 6, 7, 9, 11, 40-42). In addition, female sex and advanced age are associated with more invasive disease and worse prognosis (1, 6, 7, 11, 40-42). However, patient sex and age were not found to be independent prognostic factors of survival after diagnosis in any of our analyses. This unexpected outcome can likely be explained by differences in study design and methods. Perhaps limiting our study sample to a single stage lessened the prognostic significance typically observed for patient sex and age.

We recognize the limitations of our study design. The analysis dataset was restricted to information provided from the eight collaborating institutions. As the study population represents a series of institution-based samples, we must exercise caution when drawing conclusions about true geographic differences in T2 GBC survival; it is possible that the included cases are not representative of all T2 GBC cases. On the other hand, our study was able to overcome many limitations of the studies that are based on cancer registry data, in which inconsistent diagnostic criteria and inadequate tissue sampling may influence the findings. Cancer registry data is likely to under-stage cancers due to inadequate tissue sampling that misses the areas of deepest invasion.

Although results from this study show that geographic variation in GBC prognosis cannot be solely explained by the disparities in the stage at diagnosis, we cannot determine the relative contribution of the various other prognostic factors to differences in survival. It is possible that some of the geographic variation in GBC survival among the included countries is attributable to differences in prevalence of prognostic factors, access to appropriate surgical treatment and curative resection, and diagnostic and management practices. Future studies should focus on different mechanisms of carcinogenesis and clinical practices that may be in play in different geographic regions.

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TABLES AND FIGURES

Table 1. Demographic characteristics of patients with T2 GBC from collaborating institutions

Patient Characteristic		Geographic Region, n (%)			
		USA	**Chile**	**South Korea**	**Total**
Sex	Female	52 (70)	119 (87)	59 (56)	230 (73)
	Male	22 (30)	18 (13)	46 (44)	86 (27)
	Total	74 (23)	137 (43)	105 (33)	316 (100)
Age, years	≤ 60	27 (36)	39 (28)	35 (33)	101 (32)
	61-70	24 (32)	45 (33)	36 (34)	105 (33)
	>70	23 (31)	53 (39)	34 (32)	110 (35)
	Total	74 (23)	137 (43)	105 (33)	316 (100)

Table 2. Multivariable survival analyses assessing independent associations of age, sex, and geographic region with five-year all-cause mortality among T2 GBC patients

Variables		HR (95% CI)	p-value
Geographic region	South Korea	Reference	
	USA	1.75 (1.12-2.75)	0.015
	Chile	1.89 (1.27-2.83)	0.002
Sex	Female	Reference	
	Male	1.37 (0.95-1.97)	0.096
Age, years	≤ 60	Reference	
	61-70	1.10 (0.72-1.68)	0.652
	>70	1.34 (0.90-2.01)	0.152

Table 3. Multivariable survival analyses assessing independent associations of age, sex, and geographic region with five-year disease-specific mortality among T2 GBC patients

Variables		HR (95% CI)	p-value
Geographic region	South Korea	Reference	
	USA	1.94 (1.14-3.31)	0.015
	Chile	2.41 (1.51-3.84)	<0.001
Sex	Female	Reference	
	Male	1.34 (0.88-2.04)	0.171
Age, years	≤ 60	Reference	
	61-70	1.25 (0.78-2.00)	0.358
	>70	1.24 (0.78-1.99)	0.361

Figure 1. Kaplan-Meier curve of one-year, three-year, and five-year overall survival for T2 GBC patients (n = 316) by geographic cohort

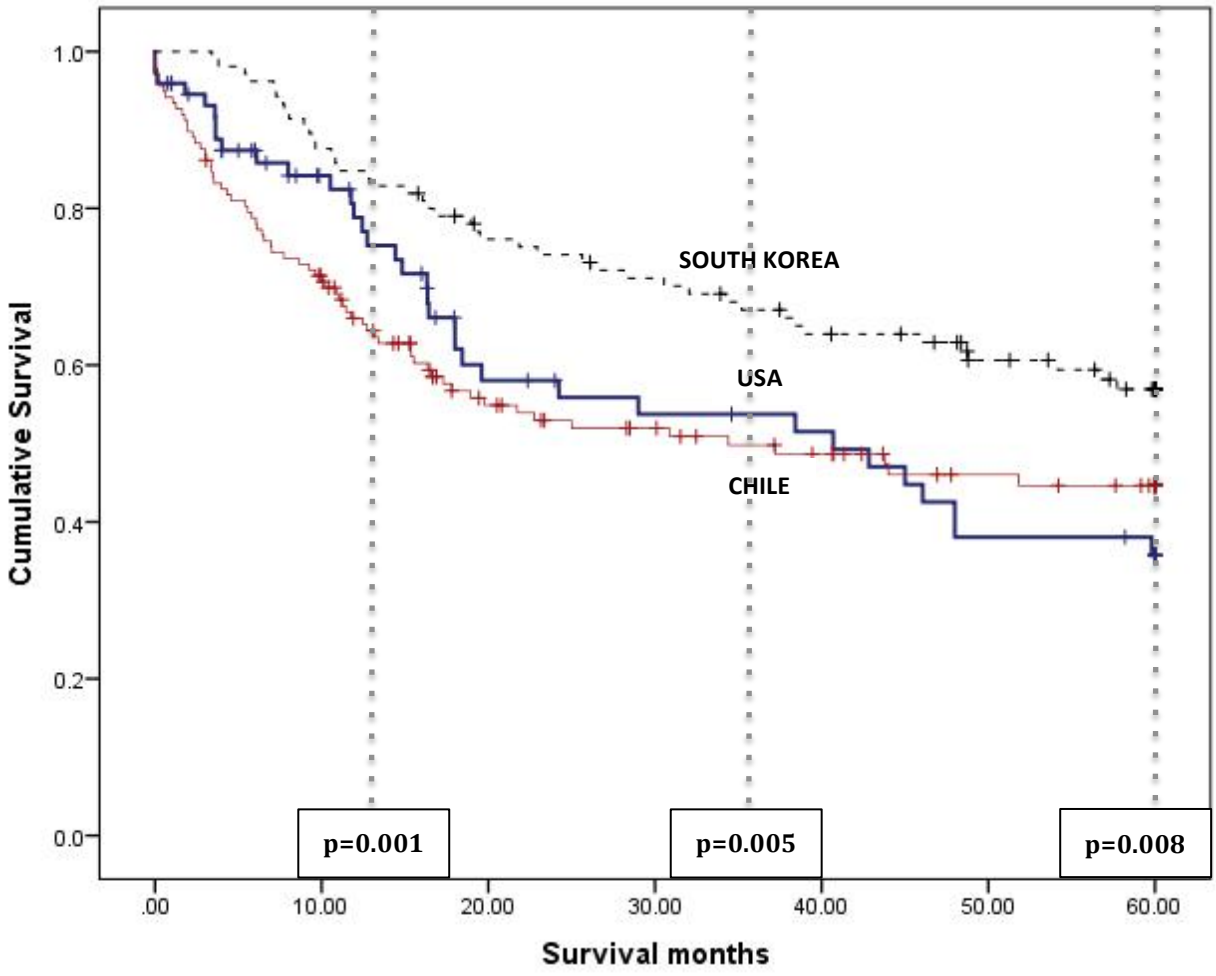
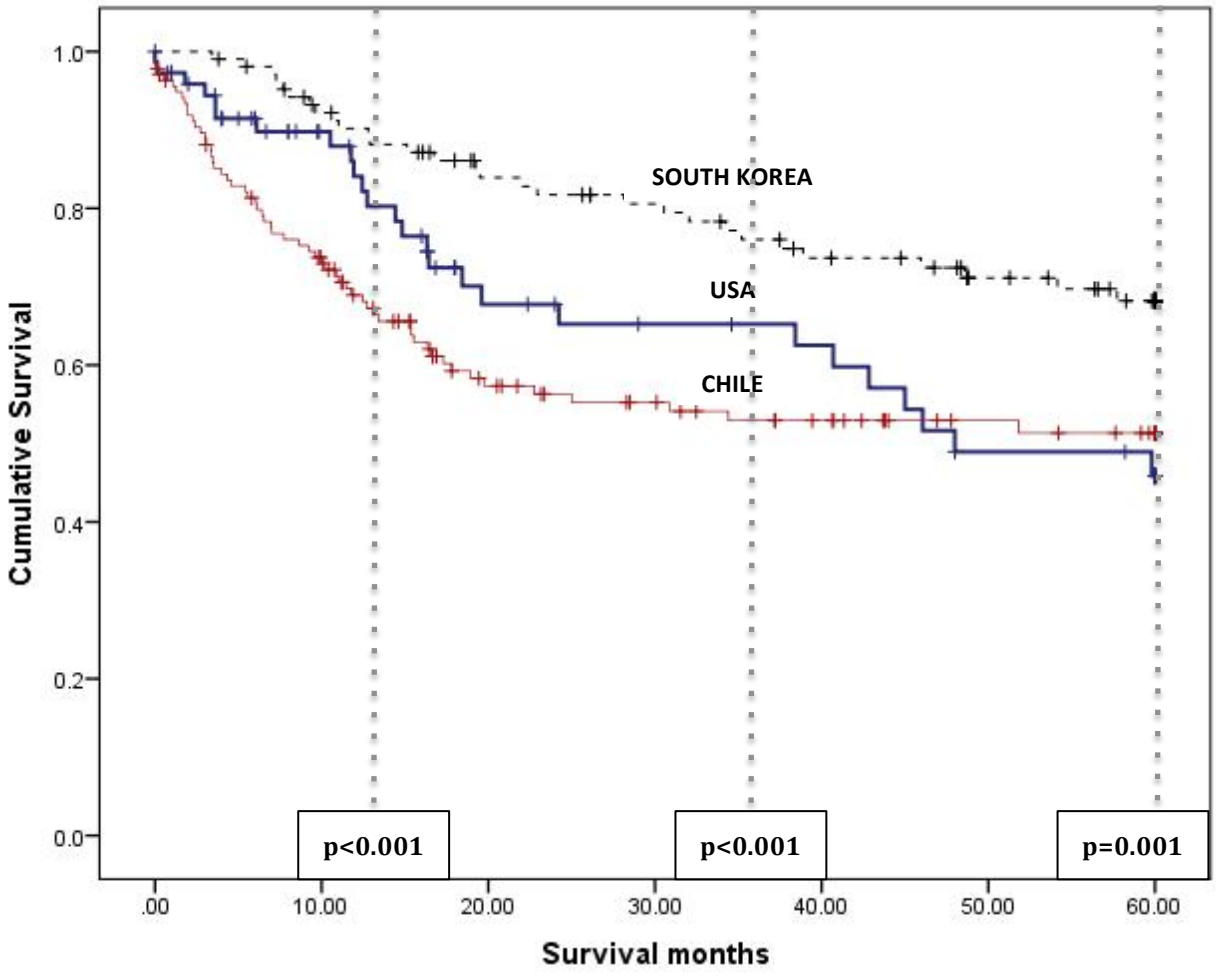


Figure 2. Kaplan-Meier curve of one-year, three-year, and five-year disease-specific survival for T2 GBC patients (n = 316) by geographic cohort



CHAPTER 4:
CONCLUSION AND RECOMMENDATIONS

Major Findings

In this study, we compared post-diagnosis overall and disease-specific survival among 316 patients with histologically proven T2 GBC from eight collaborating institutions in three countries: Chile, South Korea, and the USA. The overall survival varied significantly by geographic site, with South Korea consistently demonstrating the highest survival across the entire follow-up period. The differences in disease-specific survival were generally similar to those seen with overall survival. Compared to patients from South Korea, patients from Chile had a significantly worse prognosis with respect to overall and, in particular, disease-specific survival. The corresponding differences between South Korea and the USA were less pronounced. Patient sex and age were not associated with prognosis in either analysis.

Conclusion

The results of this large, international, multicenter cohort study demonstrate that even after limiting the comparisons to patients with confirmed T2 stage, there are notable geographic differences in GBC survival. It is possible that some of the geographic variation in GBC survival among the included countries is attributable to differences in prevalence of prognostic factors, access to appropriate surgical treatment and curative resection, and diagnostic and management practices. We hypothesize that variability in the histopathologic criteria also plays an essential role. Although recent literature has evaluated the geographic variations in GBC survival among institutions in different countries, the present study is the first international, multicenter collaboration to specifically examine the geographic variations in survival within a single GBC tumor stage that is carefully characterized and adequately sampled.

Recommendations

We believe the next step in clarifying the geographic variation in survival and prognosis is first to examine the prognostic value of pathologic sub-staging of T2 GBC and then validate and integrate these new sub-staging criteria into future guidelines for GBC staging. These steps should lead to the development of a more internationally accepted, practical, and relevant diagnostic criteria for GBC.

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