

Comparative incidence of incidental gallbladder cancer in emergency cholecystectomies *versus* in elective cholecystectomies.

Incidência comparativa de câncer incidental de vesícula biliar em colecistectomias de urgência versus colecistectomias eletivas.

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ABSTRACT

Objective: to comparatively analyse the incidence of incidental gallbladder cancer in emergency cholecystectomies *versus* in elective cholecystectomies performed in public hospitals in Teresina city, Piauí state (PI). **Methods:** descriptive, quantitative, observational, cross-sectional study, whose scenarios were two public hospitals in Teresina-PI. We analysed 6,329 medical records of patients undergoing cholecystectomy between January 2011 and December 2017. The collected data were divided into two groups and statistically compared using Z-test for difference between proportions. **Results:** incidental gallbladder cancer was detected in 6.53% of emergency cholecystectomies and in 0.38% of elective ones. Regarding gender, it was observed that in emergency surgeries 69% of patients were women and 31% men, while in elective procedures 78% were women and 22% men. Regarding age, most patients were over 60 years old, and, among these, 69.3% underwent emergency cholecystectomies and 82.6% underwent elective cholecystectomies. The histopathological type "adenocarcinoma" was found in 84.6% of patients who underwent emergency surgeries and in 100% of patients who underwent elective surgeries. **Conclusion:** incidental gallbladder cancer was more frequent in urgent cholecystectomies compared to elective cholecystectomies. The profile of patients with this malignant disease in both types of procedure was female, older than 60 years, and with histopathological diagnosis of adenocarcinoma.

Keywords: Cholecystectomy. Gallbladder Neoplasms. Gallbladder.

INTRODUCTION

Gallbladder cancer is a rare tumor with high mortality rates. It is the cancer that occurs in the bile ducts with the lowest median survival at the time of diagnosis, the most common bile duct cancer, and the fifth most common among gastrointestinal cancers^{1,2}.

In the vast majority, patients are asymptomatic or have nonspecific symptoms, such as nausea, abdominal pain, or weight loss, which are similar signs to those presented by patients with benign gallbladder disease, which makes early diagnosis difficult. Only 30% of gallbladder carcinomas are suspected preoperatively, while the others are discovered incidentally during or

after cholecystectomy³. The incidence of incidental gallbladder cancer has significantly increased and is currently the most frequent presentation of this entity, with diagnosis established by histopathological examination of the surgical specimen⁴.

Among the factors related to the etiopathogenesis of gallbladder cancer, lithiasis, mainly in coexistence with gallbladder mud, is present in 96% of patients, being the main risk factor⁵. Obesity, chronic inflammation, female gender, age greater than 65 years, Asian or African-American ethnicity, and high preoperative alkaline phosphatase values are also related to a higher incidence of gallbladder cancer⁶.

Despite the increase in the diagnosis of these incidental carcinomas, most are diagnosed in advanced stages⁴. Therefore, when, at the

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time of surgical exploration, the disease is considered unresectable, which occurs in most cases, palliative procedures should be considered⁷. Thus, surgeons should be prepared to deal with incidental gallbladder cancer, offering the most convenient management according to the findings. In addition, it becomes relevant to note that late diagnoses, particularly those related to inadequate histopathological study or non-compliance in the postoperative period, are associated with low survival rates, and this stands out with regard to the elaboration of measures related to medical education and better care for these patients.

This study seeks to comparatively analyse the incidence of incidental gallbladder cancer in emergency cholecystectomies *versus* in elective cholecystectomies performed in public hospitals in Teresina-PI, as well as to highlight the most affected age group and gender and describe the most common histopathological type.

METHODS

This is a descriptive, quantitative, observational, cross-sectional study to analyse, through data collection from medical records, aspects related to incidental gallbladder cancer in emergency and elective cholecystectomies. It was developed in accordance with Resolution 466/2012 of the National Health Council (CNS), which defines the guidelines and regulatory standards of researches in Brazil, involving mainly human beings. The project was only started after being analysed and approved by the Research Ethics Committees of Facid Faculty, opinion CAAE n# 88134318.0.0000.5211, and of the hospitals related to this work, and through the

signing of the Data Use Commitment Term by the heads of the institutions in which the research was conducted.

The study was carried out in two reference public hospitals in Teresina-PI, as they are important surgical and research centers, from January 2011 to December 2017. As inclusion criteria, we used the medical records of all patients who underwent emergency or elective cholecystectomy during the study period. Exclusion criteria were: medical records of patients with previous diagnosis of gallbladder cancer, medical records of patients who underwent other surgeries and occasionally had the gallbladder removed, or medical records which were inadequately or insufficiently filled out.

Data collection was performed using a data collection form covering the following variables: age group, gender, ICD-10 (International Classification of Diseases), and anatomopathological outcome, and patients were divided into two groups: group A, which included patients undergoing elective cholecystectomies performed at hospital 1, and group B, which included patients undergoing emergency cholecystectomies performed at hospital 2.

Regarding statistical analysis, data were organized in Microsoft Office Excel 2010 spreadsheets and presented as graphs and tables. In addition, data corresponding to each technique were confronted, comparing the analysed variables in order to demonstrate statistically significant differences in the results between elective and emergency surgeries. For this, Z-test for difference between proportions was used through R-Statistics (version 3.4.4), with confidence interval of 95% and statistical significance of $p < 0.05$.

RESULTS

During the study period, 7,112 patients underwent elective and emergency cholecystectomies, of which 6,329 were included in the analysis. Of these, 5,931 underwent elective cholecystectomy and 398 underwent emergency cholecystectomy. Among these latter, 26 (6.53%) presented postoperative diagnosis of gallbladder cancer through anatomopathological examination (Table 1).

Regarding the anatomopathological findings referring to the 5,931 patients who underwent elective cholecystectomy, it is observed that 23 (0.38%) patients had gallbladder cancer (Table 2).

When comparing the data collected through Z-test for proportions, it is observed that there was a significant difference between the incidence of gallbladder cancers diagnosed after emergency cholecystectomy *versus* the incidence of gallbladder cancers diagnosed after elective cholecystectomy ($p < 0.05$). The disease was more common after emergency surgery.

Regarding gender, of the 26 patients diagnosed with incidental gallbladder cancer after emergency cholecystectomy, 18 (69%) were female and eight (31%) male ($p = 0.0055$). Considering the 23 patients diagnosed with incidental gallbladder cancer after elective cholecystectomy, 18 (78%) were female and five (22%) male ($p = 0.00013$).

Table 1. Distribution of gallbladder diseases after emergency cholecystectomies.

Anatomopathological findings	Total	
	N	%
Gallbladder cancer	26	6.53
Porcelain gallbladder	2	0.52
Chronic cholecystitis in sclero-atrophic gallbladder	3	0.8
Mucous polyp	5	1.25
Chronic cholecystitis with areas of fibrosis and calcification	6	1.5
Chronic cholecystitis	95	23.8
Chronic cholecystitis with acute areas	125	31.4
Acute cholecystitis	136	34.2
Total	398	100

Table 2. Distribution of gallbladder diseases after elective cholecystectomies.

Anatomopathological findings	Total	
	N	%
Gallbladder cancer	23	0.38
Porcelain gallbladder	2	0.05
Chronic cholecystitis in sclero-atrophic gallbladder	5	0.1
Acute cholecystitis	8	0.2
Chronic cholecystitis with areas of fibrosis and calcification	38	0.55
Mucous polyp	43	0.72
Chronic cholecystitis with acute areas	102	1.8
Chronic cholecystitis	5,710	96.2
Total	5,931	100

When comparing the data of the most affected gender in emergency cholecystectomies versus the ones in elective cholecystectomies, it is possible to conclude that, although the samples had different values, there was no statistically significant difference ($p=0.4749$), so it could not be stated if the female gender was more affected in the emergency or elective surgeries (Figure 1).

For the analysis of age range, groups were divided with cutoff criteria: 0 to 30 years, 31 to 60 years, 61 to 70 years, 71 to 80 years, and over 80 years. Of the 26 patients undergoing emergency cholecystectomy who had anatomopathological diagnosis of gallbladder cancer, one (3.8%) was in the range of 0 to 30 years, seven (26.9%) in

the range of 31 to 60 years, eight (30.8%) were between 61 and 70 years, four (15.4%) were in the range of 71 to 80 years, and six (23.1%) were over 80 years old.

Regarding the 23 patients diagnosed with incidental gallbladder cancer after elective surgery, four (17.4%) were between 31 and 60 years, 11 (47.8%) were between 61 and 70 years, five (21.7%) belonged to the age group between 71 and 80 years, and three (13.1%) were over 80 years old.

Comparing the ages of patients undergoing emergency cholecystectomies and elective cholecystectomies, it was evident that there was no statistically significant difference between them ($p=0.2771$) (Figure 2).

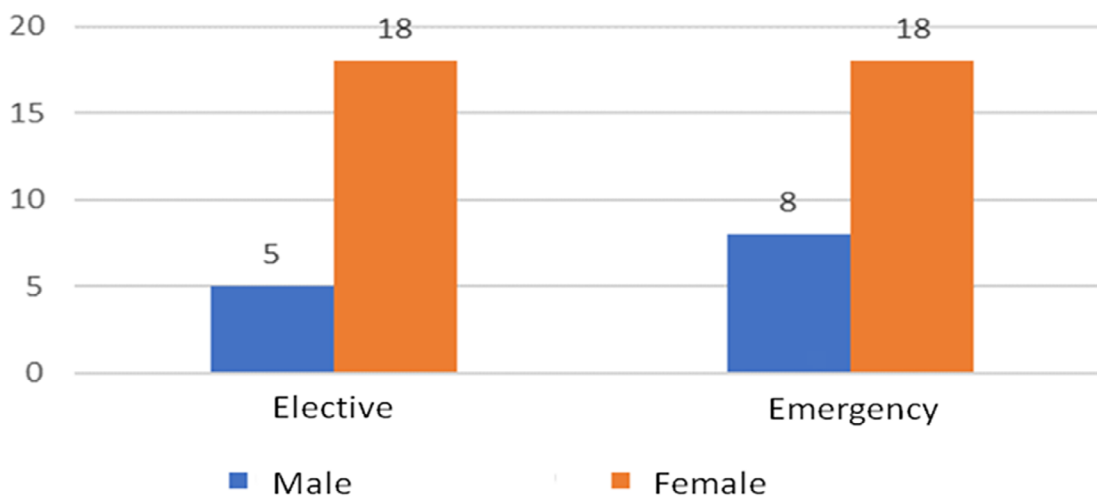


Figure 1. Gender distribution of patients with incidental gallbladder cancer.

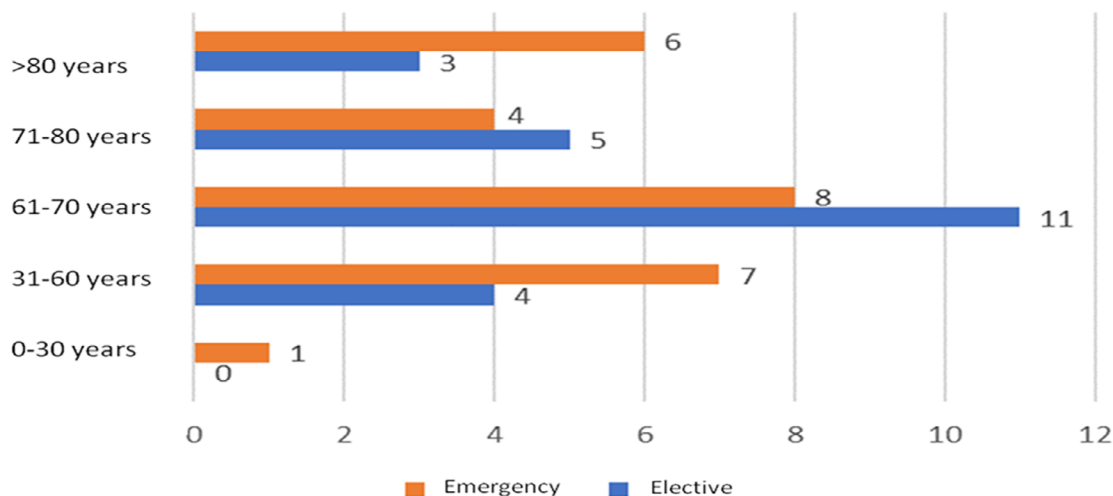


Figure 2. Age distribution of patients with incidental gallbladder cancer.

Regarding the histopathological type, of the 26 incidental gallbladder cancers after emergency cholecystectomy, four (15.4%) were squamous cell carcinomas and 22 (84.6%) were adenocarcinomas, being one (3.85%) metastatic, 16 (61.5%) poorly differentiated, four (15.4%) moderately differentiated, and one (3.85%) well-differentiated. When comparing the histopathological types identified in the diagnosis of cancer patients after emergency cholecystectomies, it was observed that the most common one was poorly differentiated adenocarcinoma ($p=0.00063$).

Of the 23 patients with gallbladder cancer after elective cholecystectomy, all had adenocarcinomas, being one (4.35%) mucinous, two (8.7%) papillary, three (13%) poorly differentiated, ten (43.5%) moderately differentiated, and seven (30.45%) well-differentiated. Relating the histopathological types, it was observed that, although there was a sample difference between moderately differentiated adenocarcinoma and well-differentiated adenocarcinoma, which were the two most commonly found, both were equally considered the most prevalent ($p=0.3595$). When comparing these two histopathological types with the others, there

was a statistically significant difference ($p=0.0012$), confirming that they were the most common.

The most common histopathological type, both in cancers diagnosed after emergency cholecystectomies ($p<0.05$) and in those evidenced after elective surgeries, was adenocarcinoma, and, when comparing the most prevalent data of emergency cholecystectomy *versus* the ones of elective cholecystectomy, it could be stated that there was a statistically significant difference ($p=0.049$), so that elective surgery had a higher incidence of adenocarcinoma when compared to emergency surgery (Figure 3).

DISCUSSION

Although rare, gallbladder cancer is responsible for 80% to 95% of cases of malignant diseases involving the biliary tract, being the most common cancer in this region⁸. Nevertheless, few studies have been reported on gallbladder cancer-related aspects, as it is still relatively rare in western countries⁹. In this context, the histopathological examination of gallbladder specimens is an important step to confirm the diagnosis¹.

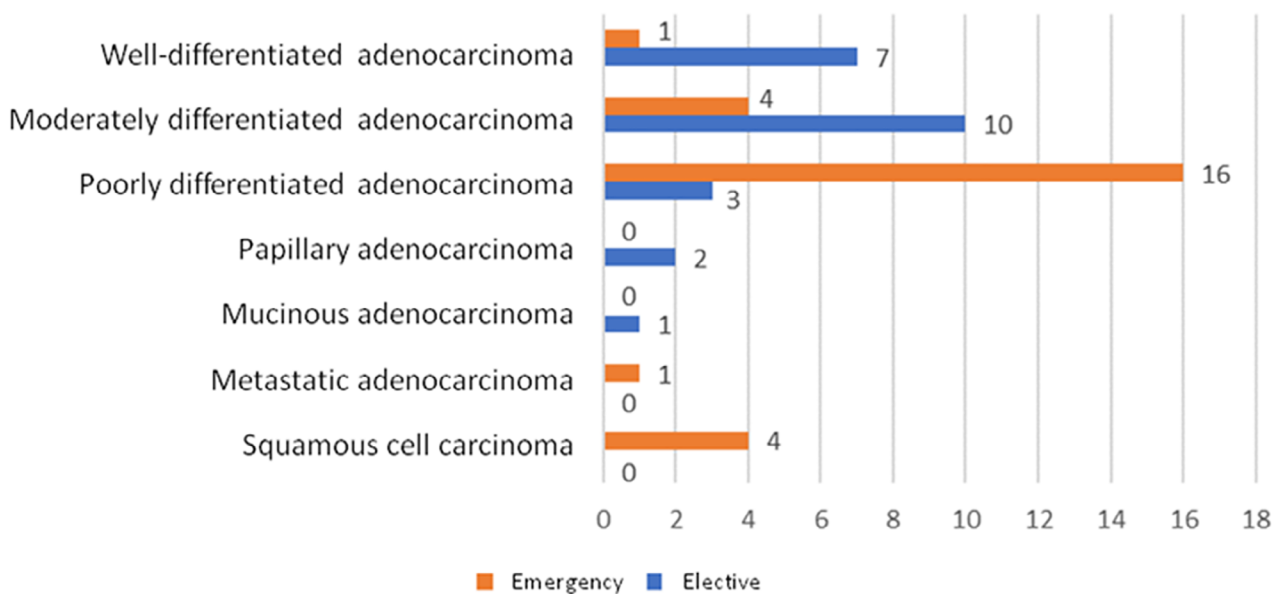


Figure 3. Distribution by histopathological type of incidental gallbladder cancer.

Data regarding the diagnoses of cancer after emergency cholecystectomy are consistent with most of literature, such as the study by Noriega Usi *et al.*¹⁰, which has evaluated 903 cholecystectomies performed over five years and found an incidence of incidental gallbladder cancer of 0.4%. The rates related to elective surgery corroborate the data found in most of world literature, such as the study by Meirelles-Costa *et al.*¹¹, which has shown that the occurrence of incidental gallbladder cancer can vary from 0.3% to 2% of all cholecystectomies performed under benign conditions.

Evidence that this disease is more common after emergency cholecystectomy has also been shown in other studies, such as the one by Torres *et al.*¹², which has suggested that prolonged chronic gallbladder stress, which occurs in symptomatic patients who are submitted to emergency surgery, increases the exposure time to oncogenes and the degree of epithelial dysplasia.

Regarding the most affected gender, it is possible to observe in a statistically significant manner that females have higher incidence in both surgical procedures, as shown in the study by Ishak *et al.*¹³, in which gallbladder cancer has represented, among women, a 79% rate. Dincel *et al.*¹, in their research, have shown that females have a four times higher frequency of gallbladder cancer when compared to males. The study by Salazar *et al.*¹⁴ has also demonstrated that there is higher incidence and higher mortality coefficient in females.

The increased risk of gallbladder cancer in women is explained by the higher incidence of cholelithiasis in women when compared to men. In addition, longer exposure to female sex hormones may also be a predisposing factor. Therefore, younger menarche age, early first pregnancy, multiple pregnancies, and prolonged reproductive period, as these are situations of prolonged exposure to hormonal agents, may also increase the risk of

biliary tract cancer¹¹. In addition, women seek care more often than men and this may justify the higher incidence in females.

Regarding age range, most of literature is in agreement with what is evidenced here, as the study by Tian *et al.*¹⁵, which has concluded that the average of incidental gallbladder cancer patients' age has been 61 years, and the research by Pais-Costa *et al.*⁹, which has evidenced that the average of incidental gallbladder cancer patients' age has been 71 years.

The study by Meirelles-Costa *et al.*¹¹ has also demonstrated that the incidence of precancerous lesions, as well as of cancer, should increase with age, due to longer exposure time to mutations and oncogen production, with the highest incidence occurring among patients over 60 years, confirming what is shown in this research. Aging is also associated with a longer exposure to risk factors, such as infections, adenoma-carcinoma sequence, obesity, and activation of genetic factors, which increase the probability of incidental cancer diagnosis.

Finally, this study shows that the most common histopathological type is the adenocarcinoma, which is in agreement with what is evidenced in most of literature, as in the studies by Kalita *et al.*¹⁶, which have shown that, of the 18 incidental gallbladder cancers found, 15 have been adenocarcinomas, and in the study by Apodaca-Rueda *et al.*¹⁷, which has revealed adenocarcinoma in 90% of incidental gallbladder cancer cases.

Therefore, we conclude that incidental gallbladder cancer has higher incidence in emergency surgery when compared to elective surgery, and that, in both surgical analysed modalities, cancer is more frequent in females and in patients over 60 years, being the adenocarcinoma the most common histopathological type. Occasional

finding of gallbladder cancer is more common than imagined, and this reinforces the importance of outpatient return with revision of the histopathological

examination of the gallbladder, since the absence of this measure is associated with the diagnosis of late and advanced gallbladder cancer, with low survival rates.

R E S U M O

Objetivo: analisar, comparativamente, a incidência de câncer incidental de vesícula biliar em colecistectomias de urgência versus colecistectomias eletivas realizadas em hospitais públicos de Teresina-PI. **Métodos:** estudo observacional descritivo, quantitativo, com delineamento transversal, cujo cenário foram dois hospitais públicos de Teresina-PI. Foram analisados 6.329 prontuários de pacientes submetidos à colecistectomia, entre janeiro de 2011 e dezembro de 2017. Os dados coletados foram divididos em dois grupos e confrontados estatisticamente através do teste Z para diferença entre proporções. **Resultados:** detectou-se câncer incidental da vesícula biliar em 6,53% das colecistectomias de urgência e em 0,38% das eletivas. Quanto ao sexo, observou-se que, na cirurgia de urgência, 69% eram mulheres e 31%, homens, enquanto no procedimento eletivo, 78% eram mulheres e 22%, homens. Quanto à idade, a maioria dos pacientes possuía mais de 60 anos e, entre estes, 69,3% submetidos à colecistectomias de urgência e 82,6%, à eletivas. O tipo histopatológico "adenocarcinoma" foi encontrado em 84,6% das cirurgias de urgência e 100% das eletivas. **Conclusão:** câncer incidental de vesícula biliar foi mais frequente em colecistectomias de urgência em comparação às eletivas. O perfil dos pacientes com essa doença maligna nos dois tipos de procedimento foi do sexo feminino, maiores de 60 anos de idade e com diagnóstico histopatológico de adenocarcinoma.

Descritores: Colecistectomia. Neoplasias da Vesícula Biliar. Vesícula Biliar.

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Received in: 09/25/2019

Accepted for publication: 10/29/2019

Conflict of interest: none.

Source of funding: none.

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