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A single-center experience

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Predictive factors for incidental gallbladder cancer (IGBC) in patients undergoing cholecystectomy for presumed benign disease. A single-center experience

AIM: *The incidence of incidental gallbladder cancer (IGBC) is estimated at 0.3-2.1%. The purpose of our study is to evaluate IGBC incidence in our department and to establish its predictive factors, considering patients' clinical characteristics and pre-operative ultrasound gallbladder features.*
MATERIAL OF STUDY: *From January 2012 to December 2015, 434 patients (225 females and 209 males) were enrolled in this retrospective observational study in our General Surgery Department. To analyze potential predictive factors, we divided all the patients into two groups: patients with and without histological diagnosis of IGBC. We focused our attention on the patients' clinical characteristics and preoperative ultrasound gallbladder measurements*
RESULTS: *Seven cases were post-operatively identified as incidental gallbladder cancer (IGBC) and after histological examination an IGBC incidence of 1.6% was encountered.*
DISCUSSION: *Considering the increasing numbers of video laparoscopic cholecystectomies (VLC) performed worldwide, cases of IGBC are appearing more frequently. In most cases of IGBC, a second surgical look will be necessary because of feasibility and safety procedures.*
CONCLUSIONS: *There is no possibility to establish which risk factors might be predictive for IGBC because of a discordance in the literature and a statistical analysis with low sample size. An accurate surgical procedure needs to be performed to reduce the spread of neoplastic cells and, as a result, improve long-term outcomes.*

KEY WORDS: Incidental Gallbladder cancer, Laparoscopy, Ultrasound

Introduction

Incidental gallbladder cancer (IGBC) is an uncommon cancer which is incidentally diagnosed during or after cholecystectomy on pathological examination. Incidental gallbladder cancer (IGBC) incidence is estimated at 0.3-2.1% [1-3].

Gallbladder cancer is the most common of biliary tract cancers. Worldwide incidence of gallbladder cancer is 1-2% and rates rise with age with two peaks of incidence, the first occurring at 50-60 years of age and the second one occurring at 70-80 [5-7]. Gallbladder cancer is more often diagnosed in female than male patients (ratio 3:1). Cholelithiasis is the most common risk factor. One case-control study, conducted in China involved 368 patients with gallbladder cancer and 959 patients as healthy controls. This study showed that patients with symptomatic gallbladder (gallstones or cholecystitis) had a 34 times higher risk of developing gallbladder cancer . However among patients affected by cholelithiasis, the incidence of gallbladder cancer is between 0.5 and 3% . Gallstone

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size increased risk and patients with gallstones >3cm showed a risk ratio 10 times higher than patients with gallstones <1cm [10].

Another factor to be considered is the presence of cholelithiasis, especially when the patient is over 40 years of age [11]. Chronic inflammation may also be related to malignant transformation as it damages DNA and activates DNA repair processes. Activated cytokines and growth factors influence cellular transformation, because if DNA repair fails and apoptosis is not activated, irreparable DNA damage may occur, leading to malignancy growth [12]. The role of gallbladder polyps in carcinogenesis remains unclear [13] although large polyps present a high risk of turning into invasive carcinoma.

Several studies suggest a correlation between the presence of gallbladder polyps and gallbladder cancer risk [14]. *Salmonella* and *Helicobacter* infections [15,16] are also risk factors for chronic inflammation and for DNA damage with almost 6% of typhoid patients d developing gallbladder cancer, a 12-fold increase in risk [12] while obesity and smoking are also considered predisposing factors [12]. It is therefore important to reach a correct diagnosis before surgery to plan appropriate treatment. The purpose of our study is to evaluate IGBC incidence in our department and to establish its predictive factors while considering patients' clinical characteristics and the pre-operative ultrasound features of their gallbladders.

Materials and Methods

Between January 2012 to December 2015, 434 patients (225 females and 209 males) were enrolled in this retrospective observational study in our General Surgery Department. Inclusion criteria required patients admitted with clinical signs and symptoms of acute cholecystitis or acute abdomen or polytrauma, patients with clinical signs and symptoms of symptomatic cholelithiasis, recurrent episodes of biliary colic and/or gallstone pancreatitis. Exclusion criteria included patients in whom the diagnosis of gallbladder cancer was preoperatively suspected. Cholecystectomy was performed using laparoscopic techniques (Video Laparoscopic Cholecystectomy, henceforth VLC).Rarely, as a result of a patient's clinical condition or technical difficulties (anatomic variations and/or visceral adhesions), an Open Cholecystectomy (OC) was performed. Written informed consent was obtained from all patients.

To analyse potential predictive factors, we split the patients into two groups, namely patients with and without a histological diagnosis of IGBC.

We focused our attention on the patients' clinical characteristics and preoperative gallbladder measurements via ultrasound using a Toshiba Nemio Ultrasound Machine (Convex probe).

We recorded all data using Excel™ including age, sex, admission (elective or emergency), surgical procedure (VLC, OC), diagnosis on admission, previous episodes of biliary colic, histological diagnosis and preoperative ecographic measurements of the gallbladder (gallbladder volume, gallbladder wall thickness and the number and size of any gallstones).

As far as diagnosis on admission was concerned we considered the following diagnoses: asymptomatic cholelithiasis, acute cholecystitis, biliary colic, acute gallstone pancreatitis, obstructive jaundice, acute abdomen, gallbladder adenomyomatosis and polytrauma (a single patient requiring an emergency cholecystectomy due to trauma). For statistical evaluation purposes these diagnoses were divided into three groups: patients symptomatic for gallbladder disease; asymptomatic patients and patients with a preoperative diagnosis of obstructive jaundice and/or acute gallstone pancreatitis.

As far as ecographic measurements were concerned, we established the following values as potential predictive factors: gallbladder volume >50 ml; gallbladder wall thickness ≥ 3 mm; number of gallstones ≥ 3; gallstones size ≥ 2 cm.

Finally, we considered pathological examinations as follows: acute cholecystitis, chronic cholecystitis, IGBC and gallbladder adenomyoma.

Results

Between January 2012 and December 2015, 434 patients (225 females and 209 males) were enrolled in our General Surgery Department to undergo cholecystectomy. 7 cases were post-operatively identified as incidental gallbladder cancer (IGBC) following histological examination. IGBC has an incidence of 1,6% in our experience. The other 427 patients, whose histological examination proved negative for gallbladder cancer were considered as negative control cases. The mean age of patients with IGBC was 65 ± 7.9 years old (50-72), a total of 7 patients of whom 4 were female (57.1%) and 3 were male (42.9%). The case-control group consisted of 427 patients: 221 females (51.8%) and 206 males (48.2%) with a mean age of 56 ± 16 years old (14-97). In the IGBC group, 3 patients were over 65 years of age[17] (42.9%) and 4 (57.1%) younger than this. In the control case group, patients over 65 years old totalled 153 (35.8%) while patients younger than 65 numbered

TABLE I - *Overall Patient Characteristics*

Patients' Characteristics		IGBC group n	IGBC group %	Control group n	Control group %
Sex	male	3	42.9	206	48.2
	female	4	57.1	221	51.8
Age	> 65 yrs	3	42.9	153	35.8
	> 65 yrs	4	57.1	274	64.2

Table II - *IGBC Patient Characteristics.*

IGBC Group		N	%
Admission	Elective	5	71.4
	Emergency	2	28.6
Preoperative Diagnosis	Symptomatic	2	28.6
	Asymptomatic	0	0
	Obstructive Jaundice And/Or Gallstone Pancreatitis	5	71.4
Previous Biliary Colic	Positive	1	14.3
	Negative	6	85.7
Surgical Procedure	Vlc	6	85.7
	Oc	0	0
	Conversion	1	14.3

Table III - *The case-control group's characteristics*

Previous Gallstone Pancreatitis	Positive	196	45.9
	NEGATIVE	231	54.1
Type Of Surgery	VLC	385	90.2
	Open	31	7.2
	Conversion	11	2.6

274 (64.2%). All the data can be examined in Table I. IGBC group: 5 patients (71.4%) were admitted electively while II patients (28.6%) came via the emergency department. Furthermore, 2 patients (28.6%) had a preoperative symptomatic diagnosis for gallbladder disease (acute cholecystitis) and 5 patients (71.4%) had a preoperative diagnosis of obstructive jaundice and/or gallstone pancreatitis. Of these 7 patients only one patient reported a previous episode of biliary colic. All patients underwent VLC and in one case conversion to OC was necessary because of visceral adhesions. All the data is presented in Table II.

We enrolled 427 patients in the control group. 376 (88.1%) of these were admitted electively and 51 (11.9%) patients were hospitalized via the emergency department. 111 patients (26.0%) had a preoperative diagnosis of symptomatic gallbladder disease, 246 patients (57.6%) were asymptomatic and the remaining 70 (16.4%) had a preoperative diagnosis of obstructive jaundice and/or gallstone pancreatitis. As far as the case-control patients were concerned, 196 (45.9%) reported a previous episode of biliary colic and 231 patients (54.1%) reported at least one episode of biliary colic. 385 cholecystectomies (90,2%) were performed via laparoscopic technique and 31 (7,2%) were performed via open technique and 11 (2,6%) VLCs were converted. All the data is presented in Table III.

As far as ecographic measurements were concerned, we established the following values as potential predictive factors: gallbladder volume >50 ml; gallbladder wall thickness ≥ 3 mm; number of gallstones ≥ 3; gallstone size ≥ 2 cm.

Gallbladder Volume

Among IGBCpts, 6 patients (85.7%) had a gallbladder volume ≥50 ml while only 1 (14.3%) had a gallbladder volume <50 ml.

Among case-control patients, 241 (56.4%) presented volumes ≥50 ml while the remaining 186 patients (43.6%) had volumes <50 ml.

Gallbladder Wall Thickness

5 patients (71.4%) with IGBC had gallbladder wall thicknesses ≥3mm while 2 patients (28.6%) did not. In the case-control group, 197 patients (46.1%) had a thickness ≥ 3mm while 230 patients (53.9%) exhibited a preoperative thickness < 3mm.

Number Of Gallstones:

In the IGBC group, 5 patients (71.4%) exhibited 3 or more gallstones within the gallbladder and 2 patients (28.6%) did not. In the cntrol group, 225 patients (52.7%) showed 3 or more gallstones and 202 patients(47.3%) did not.

Gallstone Size:

Among IGBC patients, 2 cases (28.6%) exhibited gallstones with diameter ≥2cm and 5 cases (71.4%) a diameter < 2cm. Among the case-control patients, 85 patients showed diameters ≥2cm and 342 patients showed <2cm.

Statistical Analysis

Descriptive Statistics

The Aim of our study is to consider which demographic and/or ecographic features might influence IGBC's pathogenesis and we have sought to enrich the initial descriptive analysis with some inferential statistics. α[1]=0.05 has been used as the cutoff for significance to understand if there were statistically significant differences with regard to the distribution of histological diagnoses by modifying the different variables of interest[2]. Our study group of is made up of 434 patients with a mean age of 56 years. Statistical tests underlined positive correlations in the highlighted cases.

[1] α represents the level of significance of our hypothesis verification, that is, the probability of committing the first species error (rejecting the basic hypothesis of equality of the parameters being studied when it is true).

[2] To perform such tests, the Q^2 test was used and where, at the computational stage, cells with frequencies less than 5 were detected, this was folded onto the G^2 test based on the ratio of the maximum likelihood.

TABLE IV - *Distribution of the Histological Diagnosis according to the main variables examined.*

Examined variable	Pathological examination				Total	P-value
	Acute Cholecystitis	Chronic cholecystitis	IGBC	Gallbladder Adenomyoma		
Sex						
Female	24	192	4	5	225	0.991
Male	23	178	3	5	209	
Admission						
Elective	37	330	6	9	382	0.999
Emergency	10	40	1	1	52	
Surgical procedure						
VLC	42	334	7	9	392	0.862
Open Cholecystectomy	3	27	0	1	31	
Converted VLC	2	9	0	0	11	
Admission Diagnosis						
Acute cholecystitis	15	95	2	2	114	0.013
Asymptomatic cholelithiasis	25	212	0	7	244	
Biliary colic,obstructive jaundice and pancreatitis	7	63	5	1	76	
Previous biliary colic						
Positive	14	179	1	4	198	0.025
	33	191	6	6	236	
Volume > 50ml						
Negative	28	209	6	4	247	0.259
Negative	19	161	1	6	187	
Wall Thickness > 3mm						
Positive	24	168	5	5	202	0.493
Negative	23	202	2	5	232	
Number of Gallstones > 3						
Positive	30	189	5	6	230	0.263
Negative	17	181	2	4	204	
Gallstones' size > 2cm						
Positive	5	79	2	1	87	0.219
Negative	42	291	5	9	347	
Total	47	370	7	10	434	–

A histological examination's probable distribution does not seem to be influenced by our variables. As far as Admission Diagnosis is concerned, a higher frequency can be observed among patients with clinical evidence of asymptomatic cholelithiasis including acute cholecystitis in 25 patients, chronic cholecystits in 212, adenomyoma in 7 patients and none in the case of IGBC. Among patients with clinical evidence of acute cholecystitis, chronic cholecystitis was diagnosed in 95/114 cases (83.33%). The same trend can also be noted in the group of patients with clinical evidence for biliary colic, acute gallstone pancreatitis and obstructive jaundice. More attention needs to be focused on the IGBC group, because, although small in number, the evidence for a correlation with the group of patients with clinical evidence of biliary colic, acute gallstone pancreatitis and obstructive jaundice is clear. All the data is presented in Table IV.

The G^2 test reported a statistically significant result for the *Previous biliary colic group*, seemingly approximately equidistributed between positive and negative cases (198 versus 238). A statistically significant difference can be noted between the intersection of patients with a history of biliary colic (positive or negative) and their histological diagnoses with the 7 cases of IGBC falling into the group that were negative for previous biliary colic (i.e. patients who did not exhibit biliary colic).

MULTIVARIATE ANALYSIS

In this kind of work, the most suitable statistical test is a multinomial logistics regression, in that we are working with polytomic variables.

We attempted to build a model with pathological examination as the dependent variable and previous variables which proved significant. The algorithm encountered insurmountable computational problems related to the calculation of the inverse matrix. To get out of this *impasse* we developed and verified an alternative and somewhat more complex path.

We divided the main variable Pathological examination into 4 new variables and from this built up 4 statistical (Logit) models as follows:

– Acute cholecystitis VS Chronic Cholecystis, IGBC, Adenomyoma;

– Chronic Cholecystis VS Acute cholecystitis, IGBC, Adenomyoma;
– IGBC VS Acute cholecystitis, Chronic Cholecystis, Adenomyoma;
– Adenomyoma VS Acute cholecystitis, Chronic Cholecystis, IGBC

1st model (dependent variable Acute cholecystitis)

The 1st Logit model is based on Acute cholecystitis dependent variable versus all other diagnoses and considering as explanatory only the significant results in previous analyses (*Admission Diagnosis* and *Previous Biliary Colic*) and Admission (Elective or Emergency) in interaction with the *Admission Diagnosis*. The algorithm is able to provide a correct classification percentage of about 59%, which can better explain the other diagnoses than acute cholecystitis, for this model there is also a Naegelkerke R^2 equal to 0.182. All data are presented in Table V.
As far as the direct effects of the explicative variables are concerned, significant results can be noted for Biliary Colic, Obstructive Jaundice and Pancreatitis (Table VI). In this mode, a three and a half –fold (3.527) increase in the likelihood of an Acute Cholecystitis is observed about compared to the entry diagnosis considered as baseline.
Therefore, the effects (interactions) which proved significant are those of Admission Diagnosis versus Admission Elective or Emergency. All data is set out in Table VII. One can note that the effect of *Admission* intervenes in the model with Emergency exclusively as a correction of the effect of the *Admission Diagnosis* variable by modifying its effect by increasing the likelihood of an *Acute Cholecystisis* diagnosis nearly seven-fold (6.86) compared to the considered baseline, i.e. the interaction of Symtomastic Cholelithiasis versus Elective Admission when interacting with Biliary Colic, Obstructive Jaundice and Pancreatitis.

2nd model (dependent variable Chronic Cholecystitis)

The 2nd Logit model is based on the Chronic cholecystitis dependent variable versus all other diagnoses and considering as explicative only the significant results in the previous analyses (Admission Diagnosis and Previous Biliary Colic) and Admission (Elective or Emergency) analysis in interaction with Admission Diagnosis. The algorithm succeeds in providing a percentage of correct classification of just under 60%, explaining Chronic Cholecystitis better than other diagnoses, and for this model there is a Naegelkerke $\mathbf{R}^2$ of 0.171. All the data is set out in Table VIII.

TABLE V - *Confusion matrix relative to the logit regression model analysis*

		Expected results		
		Acute Cholecystitis VS Other Diagnoses		
Observed Results		**Other Diagnoses**	**Acute Cholecystitis**	**% correct classification**
Acute Cholecystitis VS Other Diagnoses	Other Diagnoses	243	144	62.8
	Acute Cholecystitis	32	15	31.9
Total %				59.4

TABLE VI - *Statistics relative to the significant single effects of the logit model in question*

Variables	$\hat{\beta}$	**E.S.**	**p-value**	**Exp** ($\hat{\beta}$)
Admission Diagnosis			0.001	
Clinic evidence of Symptomatic Cholelithiasis (baseline)				
Asymptomatic Cholelithiasis	-0.661	0.350	0.059	0.517
Biliary Colic, Obstructive Jaundice and Pancreatitis	1.261	0.446	0.005	3.527

TABLE VII - *Statistics regarding the significant interactions of the logit model in question*

Interaction effects	$\hat{\beta}$	**E.S.**	**p-value**	**Exp** ($\hat{\beta}$)
Admission Diagnosis vs Admission			0.034	
Symptomatic Cholelithiasis versus Elective (baseline)				
Asymptomatic Cholelithiasis. by Emergency	1.252	0.700	0.074	3.496
Biliary Colic, Obstructive Jaundice and Pancreatitis by Emergency	1.926	0.892	0.031	6.864

TABLE VIII - *Confusion matrix relative to the analysis with the logit model in question*

		Expected Results		
		Chronic Cholecystitis VS Other Diagnosis		
Observed Results		**Other Diagnosis**	**Chronic Cholecystitis**	**% Correct classification**
Chronic Cholecystitis VS Other Diagnosis	Other Diagnosis	24	40	37.5
	Chronic Cholecystitis	135	235	63.5
Total %		59.7		

TABLE IX - *Statistics relative to the significant single effects of the logit model in question*

Variables	$\hat{\beta}$	**E.S.**	**p-value**	**Exp** ($\hat{\beta}$)
Admission			0.003	
Symptomatic Cholelithiasis (baseline)				
Asymptomatic Cholelithiasis	0.552	0.341	0.106	1.737
Biliary Colic, Obstructive Jaundice Pancreatitis	-1.131	0.432	0.009	0.323

TABLE X - *Statistics relative to the interactions of the logit model in question*

Interaction effects	$\hat{\beta}$	**E.S.**	**p-value**	**Exp** ($\hat{\beta}$)
Admission Diagnosis VS Admission (Elective and/or Emergency)			0.091	
Symptomatic Choleithiasis vs Elective (baseline)				
Asymptomatic Cholelithiasis by Emergency	-1.234	0.683	0.071	0.291
Biliary Colic, Obstructive Jaundice Pancreatitis by Emergency	-1.343	0.864	0.120	0.261

TABLE XI - *Confusion matrix relative to the analysis with the logit regression model in question*

		Expected Results		
		Adenomyoma VS Other Diagnosis		
Observed Results		**Other Diagnosis**	**Adenomyoma**	**% Correct classification**
Adenomyoma VS Other Diagnosis	Other Diagnosis	268	156	63.2
	Adenomyoma	7	3	30.0
Total %				62.4

As far as the direct effects of the explanatory variables are concerned, the ones related to *Admission*, especially in Biliary Colic, Obstructive Jaundice and Pancreatitis (Table IX), are significant.
One can observe that a reduction in the likelihood of a *Chronic Cholecystitis* is approximately 70% (0.323) compared to the baseline (Symptomatic Cholelithiais). There are no significant effects (interactions).

3rd Model (dependent variable Adenomyoma)

The 3rd Logit model is based on the Adenomyoma dependent variable versus all other diagnoses and considering as explicative only for the significant results in the previous analyses (Admission Diagnosis and Previous Biliary Colic) and Admission (Elective or Emergency) in interaction with Admission Diagnosis. The algorithm is able to provide a correct classification percentage of approximately 62%, explaining the other diagnosis better than Adenomyoma, and a Naegelkerke $\mathbf{R}^2$ of 0.296 is also obtained for this model. All the data is set out in Table XI.
As far as the direct effects of the explanatory variables are concerned, those for *Biliary Colic*, *Obstructive Jaundice* and *Pancreatitis* (Table XII) are significant. In correspondence to this mode, an 8-fold (8.170) increase in the probability of an *Adenomyoma* is observed compared to *Symptomatic Cholelithiasis*. In addition, one can note a halving of the probability of *Adenomyoma* in the case of *Negative Previous Biliary Colic* can be noted compared to the *Positive Previous Biliary Colic* (*baseline*).

Table XII - *Statistics relative to the significant single effects of the logit model in question*

Variables	$\hat{\beta}$	E.S.	p-value	Exp ($\hat{\beta}$)
Admission Diagnosis			0.000	
Symptomatic Cholelithiasis. (baseline)				
Asymptomatic Cholelithiasis	-0.210	0.393	0.594	0.811
Biliary Colic, Obstructive Jaundice and Pancreatitis	2.101	0.548	0.000	8.170
Admission			0.000	
Positive Biliary Colic (baseline)				
Negative Biliary Colic	-0.565	0.232	0.015	0.569

Table XIII - *Statistics relative to the interactions of the logit model in question*

Interaction effects	$\hat{\beta}$	E.S.	p-value	Exp ($\hat{\beta}$)
Admission Diagnosis vs Admission (Elective and/or Emergency)			0.000	
Symptomatic Cholelithiasis vs Elective (baseline)				
Asymptomatic Cholelithiasis By Emergency	2.849	0.790	0.000	17.267
Biliary Colic, Obstructive Jaundice and Pancreatitis By Emergency	3.239	1.108	0.003	25.519

Table XIV - *Confusion matrix relative to the analysis using a logit regression model*

		Expected Results		
		IGBC VS Other Diagnoses		
Observed Results		Other Diagnosis	IGBC	% Correct classification
IGBC VS Other Diagnoses	Other Diagnosis	274	153	64.2
	IGBC	1	6	85.7
Totale %				64.5

The significant results (interactions) are those of the Admission Diagnosis vs. Admission (Elective and/or Emergency). The effect of *Admission* intervenes in the model with Emergency exclusively as a correction of the effect of the *Admission Diagnosis* variable by modifying its effect by increasing the likelihood of an *Adenomyoma* diagnosis more than 17-fold (17.26) compared to the baseline (interaction of Symptomatic Cholelithiasis versus Elective) for *Asymptomatic Cholelithiasis* and over 25-fold in cases of *Biliary Colic, Obstructive Jaundice and Pancreatitis* (25.52).

The 4th Model (dependent variable IGBC)

The 4th Logit model is based on the dependent variable IGBC versus all other diagnoses and considering as explicative only the significant findings in the previous analyses (*Admission Diagnosis* and *Previous Biliary Colic*) and Admission (Elective or Emergency) in interaction with *Admission Diagnosis*. The algorithm succeeds in providing a correct classification percentage of more than 64%, explaining the *incidental neoplasia of the gallbladder* better than the *other diagnoses* for that model, also providing a Naegelkerke $R^2$of 0.342. All data are set out in Table XIV As far as the direct effects of the explanatory variables are concerned, those for *Biliary Colic*, *Obstructive Jaundice* and *Pancreatitis* (Table XV) are significant.
In correspondence to this mode, a more than 8-fold (8.640) increase in the probability of *IGBC* is observed compared to the baseline (Symptomatic Cholelithiasis). One can also note a halving of the probability of IGBC in cases of Negative Previous Biliary Colic compared to Positive Biliary Colic (*baseline*).
The significant results (interactions) are Admission Diagnosis versus Admission (Elective or Emergency).
In particular, one can note that the effect of Admission intervenes in the Emergency model exclusively as a correction of the effect of the variable Admission Diagnosis by modifying its effect by increasing the probability of an IGBC diagnosis approximately 11-fold (11.08) compared to the baseline considered. The interaction of *Symptomatic Cholelithiasis versus Elective*) *for* Asymptomatic Cholelithiasis is more than 15 times greater in cases of Biliary Colic, Obstructive Jaundice and Pancreatitis (15.04). All data is laid out Table XVI.

TABLE XV - *Statistics relative to the single significant effects of the logit model in question*

Variables	$\hat{\beta}$	E.S.	p-value	Exp ($\hat{\beta}$)
Admission Diagnosis			0.000	
Symptomatic Cholelithiasis (baseline)				
Asymptomatic Cholelithiasis	-0.527	0.391	0.178	0.591
Biliary Colic, Obstructive Jaundice and Pancreatitis	2.152	0.527	0.000	8.604
Previous Biliary Colic			0.000	
Positive(baseline)				
Negative	-0.569	0.239	0.017	0.566

TABLE XVI - *Statistics relative to the interactions of the logit model in question*

Interaction effects	$\hat{\beta}$	E.S.	p-value	Exp ($\hat{\beta}$)
Admission Diagnosis vs Admission (Elective and /or Emnergency)			0,002	
Symptomatic Cholelithiasis vs Elective (baseline)				
Asymptomatic Cholelithiasis by Emergency	2.405	0.785	0.002	11.080
Biliary Colic, Obstructive Jaundice and Pancreatitis by Emergency	2.711	1.069	0.011	15.038

Discussion and Comments

Gallbladder cancer is a tumor with a high malignancy and poor prognosis [18], mostly affecting elderly women. Considering the increased numbers of VLCs performed worldwide, an incidental diagnosis of gallbladder carcinoma is also becoming more frequent [19]. In most cases of incidental gallbladder cancer, a proper evaluation (also employing a CT scan) and second surgical inspection will be necessary because of the feasibility and safety of the surgical procedure. Preoperative suspicion or diagnosis of IGBC can be helpful in avoiding a second surgical procedure. Thus the aim of our study is to evaluate IGBC incidence to let the surgeon choose the most appropriate approach and to establish its predictive factors by considering a patient's clinical characteristics and pre-operative ultrasound gallbladder features.

The study presents some limitations in that it is a retrospective study and the number of IGBC patients is scanty (7/434). In spite of these limitations, using statistical analysis, we were able to obtain some results. In literature, the female gender represents a factor risk for gallbladder cancer (especially in elderly patients) and for this reason IGBC should be suspected more frequently in women. In our study, the female gender is not considered as a predictive risk factor and does not present the statistical significance attributed to it by Koshenkov[20] and Ji-QiaoZhu [21].

What emerges from our study is a statistically significant correlation between the admission diagnosis and IGBC as well as between previous episodes of biliary colic and IGBC. In particular, the diagnosis of obstructive jaundice and/or pancreatitis increases the risk of IGBC about 8-fold.

On the other hand, the absence of a previous episode of biliary colic reduced the risk of a positive outcome of a histological examination for IGBC by about half. Moreover, to our great surprise, no ultrasound test evaluated can be considered a predictor, as it is not statistically significant, contradicting other studies such as that conducted in Florida [20] in which a predictive factor would appear to be the ≥3mm thickening of the gallbladder wall. With regard to the size of the gallstones, these do not appear to be a statistically significant factor our study, while in other works we have results that are contradictory between themselves. In the above-mentioned study, the size of gallstones does not prove to be a predictive factor but, contrary to this, in a study conducted in China[21] the size of gallstones ≥3cm is a predictive factor.

From those results, we can deduce that actually it is not possible to establish which risk factors may be predictive for IGBC.

As far as pathological analysis is concerned, chronic cholecystitis is the most frequent (370 patients), followed by acute cholecystitis (47 patients), adenomyomatosis (10 patients) and IGBC (7 patients). Among IGBC patients, the most recurrent histotype was adenocarcinoma (4 patients – 57,1%), followed by large cell neuroendocrine carcinoma 1 patient (14,3%), squamous carcinoma 1 patient (14,3%) and 1 patient (14,3%) with adenosquamouscarcinoma. In literature adenocarcinoma is reported as the most common IGBC histotype. Our results can be related to Paliogiannis [22], whose results about preneoplastic and neoplastic gallbladder lesions reported 1% of IGBC.

Therefore, Napolitano [23] et al reported a literature review of 51 pts with parietal metastasis of gallbladder carci-

noma after VLC without any previous suspicion of cancer and with T1 stage carcinoma. A deep knowledge of seeding mechanisms it's also necessary to avoid seeding of neoplastic cells and the surgical procedure needs to be performed accurately.

Conclusions

In conclusion we can affirm that it is impossible to establish which risk factors may be predictive for IGBC, because of discordance in the literature and the statistical analysis in our study with a scant number of patients. Therefore, it is essential to promote a surgical procedure to be performed as cleanly and accurately as possible to reduce the spread of neoplastic cells, thus improving the long-term outcome. All the removed gallbladders need to be carefully examined because in some cases a macroscopic appearance of cholecystitis can be insidious and hide an incidental carcinoma. Increasing the sample size in future research will undoubtedly improve the statistical significance of the currently small sample size and perhaps provide clues further clues as to the triggers and predisposing factors for incidental gallbladder cancer.

Riassunto

Lo scopo del nostro studio è individuare l'incidenza di IGBC nella nostra U.O. ed i suoi eventuali fattori predittivi, considerando le caratteristiche cliniche e la valutazione ecografica della colecisti. Da gennaio 2012 a dicembre 2015, presso la nostra U.O. sono stati arruolati 434 pazienti (225 femmine e 209 maschi) sottoposti a colecistectomia e successivo esame istologico della colecisti. Criteri di inclusione: pz afferenti sia in regime d'urgenza (colecistite acuta, addome acuto, politrauma), sia in regime di elezione (colelitiasi sintomatica, ricorrenti episodi di colica biliare, esiti di pancreatite da calcolosi della colecisti). Criteri di esclusione: pz con sospetto preoperatorio di carcinoma della colecisti. Il consenso informato è stato ottenuto da tutti i pz arruolati. Nella fase pre-operatoria sono stati sottoposti ad Ecografia addominale mirata allo studio della colecisti (volume della cistifellea, spessore di parete, numero e dimensione dei calcoli). Successivamente sono statisottoposti ad intervento chirurgico che generalmente prevede una procedura laparoscopica (VLC); raramente, viene eseguita una Open Cholecystectomy (OC). Per l'analisi dei fattori predittivi è stata effettuata un'analisi statistica (test G^2)che ha considerato numerose variabili: età, genere, regime di ricovero, approccio chirurgico, diagnosi d'ingresso, pregresso episodio di colica biliare, diagnosi istologica e caratteristiche ecografiche pre-operatorie. I dati ottenuti consentono di individuare una correlazione statisticamente significativa: la diagnosi d'ingresso di *ittero ostruttivo e/o pancreatite* aumenta di circa 8 volte il rischio di IGBC. Invece, l'assenza di una pregressa colica biliare riferita lo riduce di circa metà. Inoltre, nessun dato ecografico valutato può essere considerato fattore predittivo, in quanto non correlato da significatività statistica, contrariamente a quanto riscontrato in altri studi. Analizzando le diagnosi istologiche, si deduce che le più frequenti sono quelle di colecistite cronica (370 casi su 434), seguita da colecistite acuta (47pz), adenomioma (10pz) e incidentaloma (7pz). Dei 7 pazienti con IGBC, 4 (57,1%) sono adenocarcinoma in accordo con la letteratura, 1 (14,3%) carcinoma neuroendocrino a grandi cellule, 1 (14,3%) carcinoma squamoso ed 1 (14,3%) carcinoma adenosquamoso. Considerando le difficoltà di analisi e la non concordanza con la letteratura, non possiamo indicare con certezza quali siano i fattori predittivi di IGBC. Pertanto è opportuno promuovere l'esecuzione di procedure chirurgiche quanto più accurate possibile dal punto di vista tecnico, in modo tale da poter ridurre al minimo possibile il rischio di eventuale disseminazione di cellule tumorali in cavità addominale e, di conseguenza, migliorare l'outcome del paziente. Inoltre è necessario sottoporre ad esame istologico tutte le colecisti asportate poiché si potrebbe celare un IGBC.

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