



Clinicopathologic Differences between Long-Term and Short-Term Postoperative Survivors with Advanced Gallbladder Carcinoma

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Abstract. The objective of this study was to determine histopathologic factors that influence the failure or success of extended cholecystectomy and more aggressive surgery to attain long-term survival in patients with advanced carcinoma of the gallbladder. Of 46 patients with carcinoma of the gallbladder who had undergone surgical resection, 36 had advanced carcinoma invading to or beyond the subserosal layer. Among these 36 patients were 10 long-term survivors (> 5 years) and 11 short-term survivors who died of recurrence (< 37 months) after extended cholecystectomy or more extensive surgery. Factors were compared between the two groups. Significant factors observed in the long-term survivors were the depth of invasion limited to the subserosal layer ($p < 0.05$), hepatic infiltration < 5 mm ($p < 0.01$), histologic grade of papillary or well differentiated adenocarcinoma ($p < 0.01$), absent or minimal venous, lymphatic, and perineural invasion ($p < 0.01$), and lymph node metastasis limited to the hepatoduodenal ligament ($p < 0.05$). It was concluded that the patients with subserosal invasion have a hope for long-term survival by extended cholecystectomy or more aggressive surgery when hepatic infiltration and venous, lymphatic, and perineural invasion are absent or minimal, the histologic grade is papillary or well differentiated adenocarcinoma, and lymph node metastasis is limited to the hepatoduodenal ligament.

Carcinoma of the gallbladder continues to present a therapeutic challenge because it is the most common biliary tract carcinoma [1]. We and others have shown satisfactory 5-year survival rates when carcinoma is confined to the mucosa or muscularis [2, 3]. Nevin et al. [3] demonstrated a good correlation between the depth of primary tumor invasion and survival. For advanced carcinoma, however, the prognosis is poor even after aggressive surgery [4–6]. Although Nakamura et al. [7] reported two patients with 10-year survival after right hepatic trisegmentectomy for advanced gallbladder carcinoma, these cases are exceptional. The difficulty exists with advanced carcinoma where the depth of tumor invasion extends to and beyond the subserosal layer.

We have applied extended cholecystectomy as a standard procedure [2] or more aggressive surgery for patients with advanced carcinoma, and 10 patients survived for more than 5 years. It is now of great importance to know the difference in pathologic characteristics between long-term and short-term survivors. The factors affecting failure or success after extended cholecystectomy and more aggressive surgery for advanced carcinoma of the gallbladder have not yet been carefully clarified. The aim of the

present study was to examine the histopathologic features influencing the 5-year survival of patients with advanced gallbladder carcinoma.

Patients and Methods

Forty-six patients with gallbladder carcinoma who underwent surgical resection from January 1982 to December 1994 in our department at the Kyushu University Hospital were retrospectively analyzed. Among them, 10 patients had T1 tumor: cancer restricted to the mucosa ($n = 8$) or the muscle layer ($n = 2$). Of these 10 patients, 4 underwent extended cholecystectomy (cholecystectomy plus hepatic resection approximately 2–3 cm from the gallbladder bed plus lymph node dissection) with ($n = 1$) or without ($n = 3$) resection of the extrahepatic bile duct; four underwent open cholecystectomy; and two had laparoscopic cholecystectomy. None had lymphatic, vascular, or perineural invasion. All were free from lymph node metastasis and had tumor-free surgical margins. All but two patients were alive 11 months to 13 years postoperatively without recurrence. Two patients died of unrelated causes.

The remaining 36 patients had an advanced primary tumor, extending to or beyond the subserosal layer confirmed by histologic examination. Among them, 10 patients survived for more than 5 years, and 21 patients died of tumor recurrence. Of the remaining five patients, two had an operative death, two were alive 10 and 55 months after extended cholecystectomy with resection of the extrahepatic bile duct, and one was alive 12 months after extended right lobectomy at the time of this writing. The 10 patients with advanced gallbladder carcinoma who survived more than 5 years after surgery and 21 patients who died of recurrence were reviewed to examine the causes of failure and success for long-term survival.

None of the patients who survived more than 5 years underwent simple cholecystectomy, whereas simple cholecystectomy was applied to 10 of the 21 patients who died of recurrence within 15 months. Therefore to examine the pathologic features that influence survival of patients with advanced gallbladder carcinoma after extended cholecystectomy or more extensive surgery, the 10 short-term survivors who underwent simple cholecystectomy were excluded from the analysis. Thus a total of 21 patients

Table 1. Clinicopathologic features of long-term and short-term survivors.

Patient no.	Age/sex	Depth of invasion	Extent of infiltration				Lymph node metastasis ^a	Outcome	
			hinf	ly	v	pn		Survival	Months
Long-term survivors									
1	63/F	ss	1	1	1	1	no	Alive	132
2	76/F	ss	1	0	0	0	no	Dead (LC)	75
3	37/M	ss	1	1	1	0	n1	Alive	121
4	66/M	ss	0	0	0	1	no	Alive	118
5	68/F	ss	0	0	0	0	no	Alive	99
6	62/M	se	1	0	0	0	no	Alive	97
7	68/F	ss	1	0	1	0	no	Alive	95
8	20/M	ss	0	1	0	0	n1	Alive	94
9	49/M	ss	1	1	0	0	n2	Alive	65
10	63/F	ss	0	1	0	0	n1	Alive	61
Short-term survivors									
1	67/M	ss	1	1	2	1	n2	Dead	20
2	62/F	si	3	2	2	2	n2	Dead	7
3	65/M	se	2	0	0	2	n0	Dead	37
4	45/F	si	3	1	1	1	n1	Dead	6
5	48/F	si	3	3	3	3	n3	Dead	14
6	66/M	se	1	2	0	1	n2	Dead	36
7	67/M	se	1	2	2	2	n3	Dead	12
8	70/M	ss	2	2	2	2	n3	Dead	11
9	73/M	se	3	2	1	1	n1	Dead	5
10	67/M	ss	1	2	1	3	no	Dead	14
11	60/F	ss	1	3	2	1	n1	Dead	5

LC: liver cirrhosis; ss: subserosal invasion; se: serosal invasion; si: invasion to the adjacent organ other than the liver; hinf: hepatic infiltration (0–3: see Patients and Methods); ly, v, pn: invasion to lymphatic, vascular, and perineural space, respectively (0–3: see legend to Figure 2).

^aLymph node metastasis was classified according to American Joint Committee on Cancer [9].

(10 long-term survivors and 11 short-term survivors) who underwent more aggressive surgery than extended cholecystectomy constituted the basis of this study to equalize the surgical procedures as much as possible. For these 21 patients, postoperative chemotherapy (tegafur-uracil) was carried out in 4 of the 10 long-term survivors and in 5 of the 11 short-term survivors. None underwent external or intraoperative irradiation.

Medical records and resected specimens were retrospectively examined. Histologic factors reevaluated were the (1) depth of invasion (subserosa or serosa, or invasion into an adjacent organ); (2) extent of hepatic infiltration (hinf) (0, no infiltration; 1, infiltration < 5 mm; 2, 5–20 mm; 3, > 20); (3) type of tumor invasion (α , expanding growth with clear margin; β , between α and γ , and γ , invasive growth with ill-defined border); (4) venous, lymphatic, or perineural invasion; (5) and histologic grade of carcinoma according to The General Rules for Surgical and Pathological Studies on Cancer of Biliary Tract, Japanese Society of Biliary Surgery [8]. The extent of lymph node metastasis (n) was basically classified according to the American Joint Committee on Cancer Criteria [9]: 0, absence; 1, metastasis in the hepatoduodenal ligament; 2, metastasis to the peripancreatic, periduodenal, periportal, celiac, or superior mesenteric lymph node. With respect to histologic curability, the distance from the cancer to the resected stump of the cystic duct or bile duct (bw) was measured and classified (0, cancer cells are absent within 5 mm; 1, cancer cells are present within 5 mm; 2, presence of cancer at the resected margin), to the excision plane (ew; classification same as for bw), and to the resected margin of the liver (hw; classification same as for bw).

Statistical analysis was carried out using the chi-square test. The significance of each factor was also evaluated by simple and

multiple regression analysis; probability values < 0.05 were considered significant.

Results

Postoperative Long-Term and Short-Term Survival

The clinicopathologic features are shown in Table 1. Long-term survivors consisted of five women and five men with a mean (SD) age of 57 ± 17 years at the time of surgery. All survived without recurrence for more than 5 years. One died of liver cirrhosis 6 years 3 months postoperatively, and the remaining 9 were alive for 132, 121, 118, 99, 97, 95, 94, 65, and 61 months with a mean of 8.2 years after surgery. There were four women and seven men among the short-term survivors with a mean age of 63 ± 9 years. All of them died of recurrence within 37 months. No significant difference was observed in age or gender between the two groups.

Differences Between Long-Term and Short-Term Survivors

The depth of invasion (Fig. 1) was a significant factor differentiating between the long-term and short-term survivors. Of 13 patients with subserosal invasion, 9 survived for more than 5 years, whereas only 1 of 8 patients did so after extended cholecystectomy or even more aggressive surgery when the invasion reached the serosa ($p < 0.05$). With respect to hepatic infiltration, all the long-term survivors had either hinf 0 or 1. Of 15 patients with hinf 0 or 1, ten were long-term and five short-term survivors. When hepatic infiltration exceeded 5 mm (hinf 2 or 3), all six patients died of recurrence ($p < 0.01$) (Fig. 1). The type of tumor invasion tended to be expansive rather than infiltrative in the long-term survivors, but the difference was not significant.

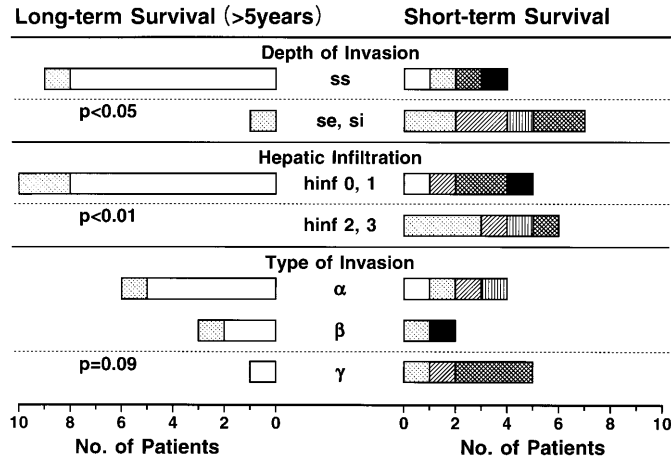


Fig. 1. Comparison between long-term and short-term survival of patients with advanced gallbladder carcinoma as a function of the depth of tumor invasion, hepatic infiltration, and type of surgery. ss: subserosa, se: serosa, si: involvement of adjacent organ other than the liver, bile duct, and major vessels. Hepatic infiltration (hinf) and type of invasion: see Patients and Methods. Type of surgical procedure: □ extended cholecystectomy (Ext Cx); ▨ Ext Cx with resection of the extrahepatic duct (BDR); ▩ hepatectomy (S4a + S5) + pancreatoduodenectomy (PD); ■ hepatic lobectomy; ▤ Ext Cx + PD; ▥ hepatectomy (S4a + S5) + BDR.

Gross and histologic features of the tumor in the long-term and short-term survivors are shown in Figure 2. The polypoid type (papillary or nodular) was more common in the long-term survivors, but the difference did not reach significance. Factors commonly observed in the long-term survivors with statistical significance were the histologic grades of papillary and well differentiated adenocarcinoma ($p < 0.01$), less extent of lymphatic, vascular, and perineural invasion ($p < 0.01$), and lymph node metastasis limited to the hepatoduodenal ligament ($p < 0.05$). As to histologic curability, all the long-term survivors had cancer-free surgical margins, as shown in Figure 2. In contrast, only 3 of the 11 short-term survivors had a tumor-free surgical margin.

The factors that significantly differentiated long-term survival from short-term survival analyzed by simple regression analysis were depth of invasion; hepatic infiltration; gross appearance; histologic grade; lymphatic, vascular, and perineural invasions; lymph node metastasis; and surgical margins (Table 2). Further analysis by multiple regression analysis showed that perineural invasion was significant ($p < 0.041$).

Discussion

The present study demonstrated that selected patients with even advanced carcinoma survived without recurrence for the long term after extended cholecystectomy. The favorable factors to predict long-term survival were (1) invasion to the subserosal layer but not beyond the serosa; (2) absent or scanty infiltration < 5 mm into the liver; (3) papillary or well differentiated adenocarcinoma; (4) absent or minimal invasion to vascular, lymphatic, and perineural spaces; and (5) lymph node metastasis limited to the hepatoduodenal ligament.

The prognosis of patients with advanced gallbladder carcinoma invading to or beyond the subserosal layer remains poor [3, 5, 6,

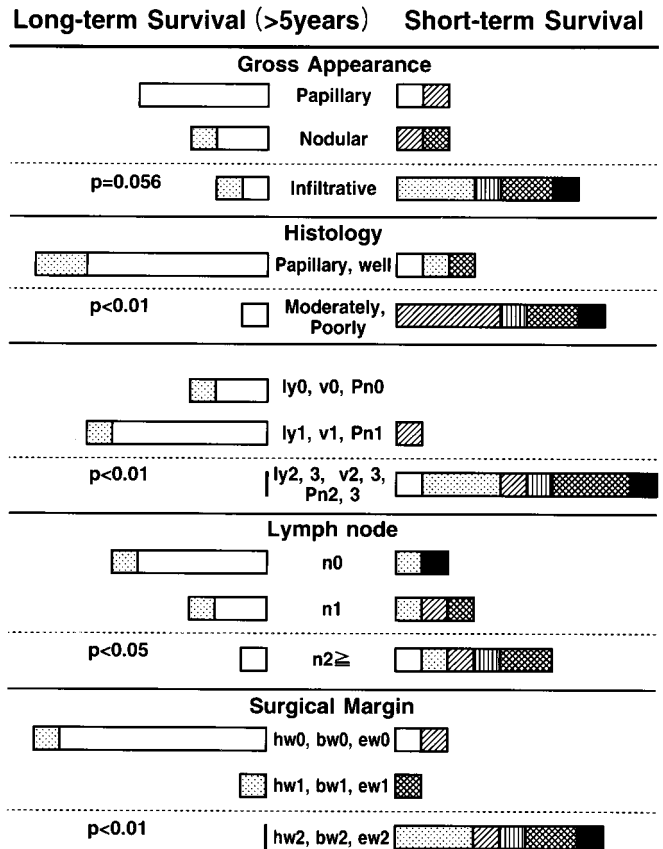


Fig. 2. Long-term and short-term survival of patients with advanced gallbladder carcinoma as a function of gross appearance, histologic grade, presence or absence of venous, lymphatic, or perineural invasion, lymph node metastasis, surgical margin, and type of surgical procedure. ly0, v0, Pn0: no invasion to lymphatic, vascular, or perineural spaces, respectively; ly1, v1, Pn1: minimal invasion; ly2, v2, Pn2: moderate invasion; ly3, v3, Pn3: massive invasion. Lymph node metastasis and surgical margin: see Patients and Methods. Type of surgical procedure: see Figure 1.

Table 2. Factors and probability values analyzed by simple regression analysis.

Factor	<i>p</i>
Depth of invasion	0.0094
Hepatic infiltration	0.0004
Type of invasion	0.1239
Histologic grade	0.0029
Gross appearance	0.0591
Lymphatic invasion	0.0006
Venous invasion	0.0024
Perineural invasion	< 0.0001
Lymph node metastasis	0.0129
Surgical margin	
Resected stump of cystic or bile duct	0.0011
Resected margin of the liver	0.0495
Excision plane	0.0010

10, 11]. Overall 5-year survival rates have been reported to be less than 5% [1, 12] based on the fact that most patients present with advanced carcinoma because of a lack of specific symptoms and signs. The satisfactory outcome has been obtained only when the depth of tumor invasion is limited to mucosa or muscularis propria [1–3]. In general, the depth of invasion has been consid-

ered to be a factor definitely influencing survival [1–3, 10, 11]. The present study focused on advanced carcinoma invading to or beyond the subserosal layer and found that the patients with subserosal invasion had significantly better survival than those with serosal involvement. Thus even those with advanced gallbladder carcinoma still have a hope for long-term survival without recurrence if the depth of invasion is limited to the subserosal layer. Hepatic infiltration of < 5 mm, if present, is another favorable factor for long-term survival.

The histopathologic grade of papillary and well differentiated adenocarcinoma is a factor predicting long-term survival, which is in concordance with other reports [1, 11, 13, 14]. The gross appearance and type of invasion of the tumor were not significant factors influencing survival, although the polypoid type in gross appearance and expanding growth with a clear tumor margin was more common in the long-term survivors. Absent or minimal invasion to vascular, lymphatic, and perineural spaces is an additional favorable factor predicting long-term survival.

Lymph node metastasis limited to the hepatoduodenal ligament was a significant ($p < 0.001$) factor distinguishing long-term survivors from short-term survivors. The extent of lymph node metastasis has been recognized as a predicting factor for survival [2, 14]. Nakamura et al. [7] reported two 10-year survivors with advanced gallbladder carcinoma who also had lymph node metastasis limited to the hepatoduodenal ligament. In the present series, 6 of 10 long-term survivors with advanced carcinoma were free from lymph node metastasis, and 3 had lymph node metastasis limited to the hepatoduodenal ligament. The remaining patient had lymph node metastasis below the pancreas head. Thus even in patients with advanced gallbladder carcinoma, surgery gives a hope for cure when lymph node metastasis is limited to the hepatoduodenal ligament. Similar observations have been reported elsewhere [2, 3, 6, 15].

With respect to the treatment of advanced gallbladder carcinoma, we applied extended cholecystectomy as a standard procedure [2]. All the long-term survivors in our series invariably had a tumor-free surgical margin. The extent of tumor invasion and lymph node metastasis definitely affected the curability of the procedure. Difficulty remains even after aggressive surgery including hepatectomy and pancreatoduodenectomy when (1) the tumor has invaded to the serosa or the depth of hepatic infiltration exceeds 5 mm; (2) histologic grade of the tumor is low; (3) vascular, lymphatic, and perineural invasion is moderate to extensive; and (4) lymph node metastasis reaches peripancreatic, celiac, superior mesenteric, and paraaortic regions.

In conclusion, advanced gallbladder carcinoma with invasion restricted to the subserosal layer has a hope for cure when hepatic infiltration and venous, lymphatic, and perineural invasions are absent or scanty and lymph node metastasis is limited to the hepatoduodenal ligament. The significance of perineural invasion necessitates further evaluation.

Résumé

But: Déterminer les facteurs histopathologiques qui influent sur l'échec ou le succès de la cholécystectomie étendue ou sur d'autres techniques chirurgicales plus agressives pour obtenir une survie à long-terme chez les patients porteurs d'un cancer de la vésicule biliaire. Méthodes: Parmi les 46 patients ayant un cancer de la vésicule biliaire réséqué, 36 avaient un cancer avancé,

envahissant la tunique sous-séreuse ou d'avantage. Chez ces 36 patients, ayant tous eu une cholécystectomie étendue ou une chirurgie plus large, on a cherché les facteurs qui différencient les dix patients avec une survie à long-terme (> 5 ans) et les 11 patients décédés de récidives (< 37 mois). Résultats: Les facteurs significatifs observés chez les patients avec survie à long terme ont été le degré d'envahissement limité à la sous-séreuse ($p < 0.05$), une infiltration hépatique de moins de 5 mm ($p < 0.01$), un adénocarcinome bien différencié ou papillaire ($p < 0.01$), l'absence d'envahissement veineux, lymphatique ou périséreuse, ou l'apparition de métastases limitées au ligament hépatoduodénal (petit épiploon) ($p < 0.05$). Conclusions: Les patients présentant un envahissement de la sous-séreuse ont une espérance de survie à long-terme lorsque l'on pratique une cholécystectomie ou une intervention plus large, à la condition qu'il n'y ait pas d'infiltration hépatique (ou une infiltration minime), veineuse, lymphatique, ou périséreuse, qu'il s'agisse de cancers bien différencié ou papillaire et que les métastases ganglionnaires soient limitées au ligament hépatoduodénal (petit épiploon).

Resumen

Propòsito: Determinar los factores histopatològicos que influyen sobre la falla o el èxito de la colecistectomìa ampliada y de la cirugía màs radical en cuanto a supervivencia a largo plazo en pacientes con carcinoma avanzado de la vesícula biliar. Métodos: De 46 pacientes con carcinoma de la vesícula sometidos a resección quirùrgica, 36 presentaban carcinoma avanzado con invasiòn hasta o màs allà de la capa subserosa. Entre estos 36 casos, se registraron 10 sobrevivientes a largo plazo (> 5 años) y 11 sobrevivientes a corto plazo que murieron de recurrencia (< 37 meses) luego de colecistectomìa ampliada o cirugía màs extensa, y se hizo la comparaciòn de diversos factores entre estos dos grupos. Resultados: Los siguientes factores aparecieron como significativos en los sobrevivientes a largo plazo: invasiòn limitada a la capa subserosa ($p < 0.05$), infiltraciòn hepàtica menor de 5 mm ($p < 0.01$), tipo histològico papilar o adenocarcinoma bien diferenciado ($p < 0.01$), ausencia o mínima invasiòn venosa, linfàtica y perineural ($p < 0.01$) y metástasis ganglionares limitadas al ligamento hepatoduodenal ($p < 0.05$). Conclusiones: Los pacientes con invasiòn subserosa tienen una expectativa real de sobrevida con la colecistectomìa ampliada o con cirugía màs radical cuando la infiltraciòn hepàtica y la invasiòn venosa, linfàtica y perineural estàn ausentes o son mínimas, el tipo histològico es papilar o adenocarcinoma bien diferenciado y las metástasis ganglionares se limitan al ligamento hepatoduodenal.

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Invited Commentary

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The authors have focused on the histopathologic factors that influence the outcome of aggressive surgery, primarily extended cholecystectomy in patients with advanced cancer of the gallbladder. They reviewed 46 patients with gallbladder cancer who underwent resection, 36 of whom had advanced cancer invading to or beyond the subserosal layer. Among these 36 patients were 10 long-term survivors (> 5 years) and 11 short-term survivors, who died of recurrence within 3 years after extended cholecystectomy or more extensive surgery, which forms the substrate for analysis in this paper. The long-term survivors had certain histopathologic features associated with better outcome, including the depth of invasion limited to the subserosal layer, and hepatic infiltration < 5 mm, as well as lymph node metastases limited to the hepatoduodenal ligament. Other factors included better differentiated tumors (papillary or well differentiated) and the absence of minimal venous, lymphatic, or perineural invasion. These factors had a significant relation to survival.

In contrast, the 11 short-term survivors had invasion reaching the serosa, as well as more invasive liver infiltration, whereas 9 of 13 patients with subserosal invasion survived more than 5 years; only 1 of 8 patients did so whose cancer invaded the serosa or beyond. Among the patients with hepatic infiltration, all of the long-term survivors had either no measurable or minimal (< 5 mm) invasion. In contrast, all six of the patients who had infiltration of > 5 mm died of recurrence. Another important surgical fact was the surgeon's ability to obtain clear margins. All

of the long-term survivors had cancer-free surgical margins, whereas only 3 of the 11 short-term survivors had clear margins. The other features associated with a good outcome included low histologic grade, favorable histomorphology (papillary, well differentiated), and tumors with minimal or absent lymphatic, vascular, and perineural invasion.

The authors have made an important contribution because they focused their data on the patients who had had extended resections, and they were able to subgroup them into those who had favorable histologic features and those who did not. Contrary to the belief of many surgeons, the significance of invasion into the subserosal wall or the liver has a major impact on survival. Authors have demonstrated the benefit of more extensive surgery compared to cholecystectomy alone: Donohue et al. [Chijiwa et al.'s ref. 6] and Shirai et al. [Chijiwa et al.'s ref. 15]. The reality of the limitations of the technique I think are most explicitly demonstrated by Dr. Chijiwa and colleagues. It appears that the minimum procedure for lesions beyond the submucosa and in the muscular layer or the subserosa is resection of the liver bed and adequate node dissection. Although more extended resections have been reported, they are not widely applicable to most of these cancers. The authors mention the success of Nakamura et al. [their ref. 7], who reported two exceptional 10-year survivors after trisegmentectomy. They are probably the exception, the reality being that the outcome for this disease is still staged-related.

I suggest that for patients with disease beyond the subserosa that extends into the subserosa with node metastases or those who have extension into the liver of > 5 mm are at high risk for recurrence even with extended resections and are candidates for adjuvant therapy. It is time that we accept a simplified adjuvant study and incorporate it into the surgical management of these patients.