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Surgical Management of Leiomyosarcoma of the Inferior Vena Cava

S. W. Cho · J. W. Marsh · D. A. Geller · M. Holtzman · H. Zeh III · D. L. Bartlett · T. C. Gamblin

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Abstract
Introduction Leiomyosarcoma of the inferior vena cava (IVC) is a rare tumor for which en bloc resection offers the only chance of cure. Due to its rarity, however, optimal strategies for the management of the primary tumor and subsequent recurrences are not well defined.
Methods We performed a retrospective review of patients who underwent surgical resection of IVC leiomyosarcoma. We evaluated clinical presentations, operative techniques, patterns of recurrence and survival.
Results From 1990 to 2008, nine patients (four females) were identified. Median age was 55 years (40–76). Presentations included abdominal pain (n=5), back pain (n=2), leg swelling (n=4) and abdominal mass (n=2). Pre-operative imaging studies showed tumor location to be from the right atrium to renal veins (n=1), retrohepatic (n=5), and from hepatic veins to the iliac bifurcations (n=3). En bloc resection included right nephrectomy (n=5), right adrenalectomy (n=4), pancreaticoduodenectomy (n=1), right hepatic trisectionectomy (n=1) and right hemicolectomy (n=1). The IVC was ligated in six patients, and a prosthetic graft was used for IVC reconstruction in three patients. Resection margins were negative in seven cases. Median length of stay was 12 days (range, 6–22 days). Major morbidity included renal failure (n=1) and there was one post-operative mortality. Five patients had leg edema post-operatively, four of whom had IVC ligation. Median survival was 47 months (range, 1–181 months). Four patients had recurrence and the median time to recurrence was 14 months (range, 3–25 months). Two patients underwent successful resection of recurrence.
Conclusions Curative resection of IVC leiomyosarcoma can lead to long-term survival. However, recurrence is common, and effective adjuvant treatments are needed. In selected cases, aggressive surgical treatment of recurrence should be considered.

Keywords Leiomyosarcoma · Inferior vena cava · Resection · Retrohepatic · Surgical resection · IVC leiomyosarcoma · Sarcoma

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S. W. Cho · J. W. Marsh · D. A. Geller · M. Holtzman · H. Zeh III · D. L. Bartlett · T. C. Gamblin
Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA

T. C. Gamblin (✉)
UPMC Liver Cancer Center,
3459 Fifth Avenue MUH 7S,
Pittsburgh, PA 15213, USA
e-mail: gamblintc@upmc.edu

Introduction

Leiomyosarcoma of the inferior vena cava (IVC) is a rare malignant tumor of the venous system. En bloc resection of the tumor is the only treatment option that can provide long-term survival.[1] However, due to its retroperitoneal location and close proximity to vital structures, careful planning is required before embarking on surgical resection. The most commonly used classification scheme dividing the IVC leiomyosarcoma into upper segment (above hepatic veins), middle segment (between hepatic veins and renal veins) and lower segment (below renal veins) reflects the importance of the major branches of the IVC in dictating operative approach and resectability of the tumor.[1] In addition, management of the IVC after tumor resection is controversial, and primary repair, ligation or reconstruction of the IVC have all been utilized with variable results.

Recurrence occurs in more than half of the patients who undergo curative resection of the IVC leiomyosarcoma.[2] Due to its rarity, however, the optimal strategy for management of recurrences is not well defined, and surgical resection, radiation therapy and systemic chemotherapy have been tried with no clear superior modality. In view of the paucity of data regarding best management of this rare tumor, we sought to evaluate our experience of surgical resection of the IVC leiomyosarcoma with particular emphasis on surgical techniques, management of recurrence and survival outcome.

Method

A retrospective review was performed of patients who underwent surgical resection of the IVC leiomyosarcoma at our institution between November 1990 and May 2008. Institutional Review Board approved the study. Clinical records were reviewed in order to obtain patient demographics, clinical presentation, pre-operative work-up, surgical techniques and morbidity as well as follow-up data on survival, patterns of recurrence and its management. Patients with retroperitoneal leiomyosarcoma originating outside the IVC and invading into the IVC were excluded from the study.

Pre-operative Work Up

All patients underwent contrast-enhanced CT scan of the chest, abdomen, and pelvis to assess resectability of the tumor and to rule out distant metastasis (Fig. 1). In addition, three patients underwent MRI of the abdomen, and three patients underwent caval venogram. Pre-operative CT or MRI scans showed the location of the tumor to be the middle segment of the IVC in five cases, middle and lower segments in three cases and upper and middle segment in one case (Table 1). Proximal extension of tumor thrombus into the right atrium in one patient was confirmed on echocardiogram. One patient had pulmonary embolism at diagnosis and a temporary IVC filter was placed pre-operatively (Fig. 2). Six patients had completely occluded IVC and three patients had partial occlusion of the IVC. All patients had extensive collateral vessels present. No patient had hepatic dysfunction from Budd–Chiari syndrome. Four patients underwent pre-operative biopsy of the tumor, which confirmed the diagnosis.

Operative Technique

Bilateral subcostal incision with upper midline extension was commonly used. First, the superior ligamentous attachments of the liver were taken down to gain access to the suprahepatic IVC and hepatic veins. The right colon was fully mobilized, and a generous Kocher maneuver of the duodenum was then performed all the way to the aorta medially, thus exposing the infrahepatic IVC and both renal veins. The lateral attachment of the hepatic right lobe was incised to expose the retrohepatic IVC. The gastrohepatic ligament was divided and involvement of the caudate lobe by the tumor was assessed. The porta hepatis was routinely encircled with a vessel loop. Short hepatic veins were ligated in order to mobilize the liver from the IVC. This allowed access to the retrocaval region. Dissection was performed in the aortocaval space freeing the aorta from the tumor. Frequently, the tumor was invading the right adrenal gland and/or right kidney, and they were resected en bloc with the tumor (Fig. 3). After clamping the IVC above and below the tumor, hemodynamic changes of the patient were assessed. In one patient, veno-venous bypass was required to maintain venous return to the heart. In one case, tumor thrombus in the right atrium required median sternotomy and cardiopulmonary bypass to remove proximal extension of the tumor before clamping the IVC just below the hepatic vein take-offs. En bloc resection of the tumor required right adrenalectomy, right nephrectomy, right hepatic trisectionectomy, pancreaticoduodenectomy, or right hemicolectomy as needed in order to achieve tumor-free margins.

In all cases, the superior resection margin of the IVC was below the level of the hepatic vein take-off. In six cases, the distal resection margin of the IVC was above the level of the renal veins. In the remaining three patients, it was below the renal veins. In all these three cases, right

Figure 1 Contrast enhanced CT scan of the abdomen. Intraluminal IVC leiomyosarcoma is visible.

Table 1 Details on Patient Demographics, Presentations, Surgical Techniques and Outcome

Patient	Gender	Age	Symptoms	Location of the tumor	Management of the IVC	EBL (in liter)	En bloc resection	LOS (in days)	Post-op morbidity	Leg Edema
1	M	55	Back pain, leg edema	Middle	Ligation	0.70	None	13	None	No
2	M	40	Abdo pain, leg edema	Middle & lower	Ligation	4.00	R nephrectomy and R adrenalectomy	12	Renal failure, hematoma	Yes
3	F	66	Abdo pain	Middle	20 mm Gore-Tex graft	0.75	R adrenalectomy	6	Atrial fibrillation	No
4	F	42	Abdo mass	Middle & lower	Ligation	0.80	none	6	None	Yes
5	F	76	Abdo pain	Upper & middle	18 mm Dacron graft	0.60	none	15	Atrial fibrillation	Yes
6	M	65	Back pain	Middle & lower	Ligation	10.00	R nephrectomy, R colectomy, pancreaticoduodenectomy	22	death	Yes
7	F	51	Abdo pain	Middle	20 mm Dacron graft	2.50	R trisectionectomy, R nephrectomy, R adrenalectomy	18	Transient hepatic encephalopathy	No
8	M	60	Abdo mass, leg edema	Middle	Ligation	1.00	R nephrectomy, R adrenalrectomy	10	None	No
9	M	53	Abdo pain, leg edema	Middle	Ligation	3.00	R nephrectomy	8	None	yes

nephrectomy was performed, and the left renal vein was ligated in two cases with venous drainage of the left kidney being maintained by collateral vessels. In one case Gore-Tex (polytetrafluoroethylene, PTFE) patch was used to reconstruct the IVC at the junction of the left renal vein.

Figure 2 IVC venogram. A temporary IVC is placed above the IVC, which is completely occluded by the tumor.

Management of the IVC after tumor resection was at operating surgeon's discretion. In all cases where a synthetic graft was used, the interposition graft was placed between the infrahepatic IVC and suprarenal IVC in an end-to-end anastomotic fashion (Fig. 4). An omental pedicle was fashioned and was used to cover the synthetic graft and prevent contact with bowel. In the patient with a deep venous thrombosis and/or pulmonary embolism,

Figure 3 Gross pathology of the IVC leiomyosarcoma (*left*). The right kidney (*right*) was also resected en bloc.

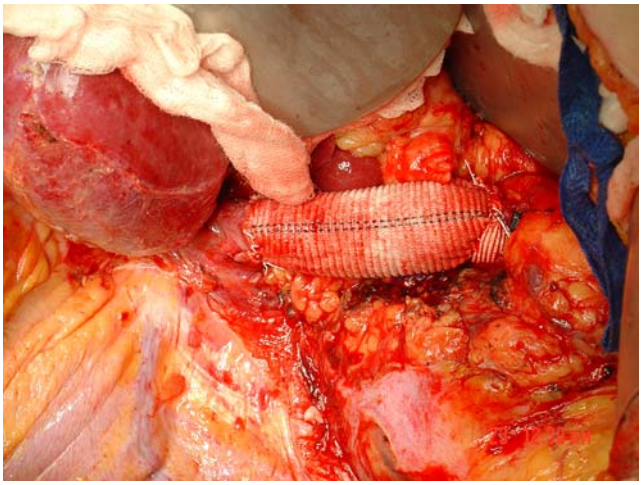

Figure 4 An operative view after the IVC reconstruction with a Dacron graft in an end-to-end anastomotic fashion.

reconstruction was not performed due to the risk of subsequent pulmonary embolism.

Results

Demographics

From November 1990 to May 2008, nine patients (four females) underwent curative resection of IVC leiomyosarcoma. Median age at presentation was 55 years (range, 40–76 years). Demographic and clinical data are shown in Table 1. Presentations included abdominal pain (n=5), back pain (n=2), leg swelling (n=4), and abdominal mass (n=2).

Surgical Procedures and Outcome

Median estimated blood loss was 1 L (range, 0.6–10 L). Median length of stay was 12 days (6–22 days). En bloc resection included right nephrectomy (n=5), right adrenalectomy (n=4), pancreaticoduodenectomy (n=1), right hepatic trisectionectomy (n=1), and right hemicolectomy (n=1; Table 2). The IVC was ligated in six patients, and a prosthetic graft was used for IVC reconstruction in three patients (two Dacron grafts, one Gore-Tex graft).

One post-operative death in our series was from hemorrhagic shock and multi-system organ failure. Major morbidity included one case of renal failure requiring temporary hemodialysis. In addition, there were two cases of atrial fibrillation, one case of retroperitoneal hematoma, and one case of transient hepatic encephalopathy. These complications were medically managed without permanent consequences. Out of six patients who had IVC ligation, four had leg edema after tumor resection, whereas only one out of three patients who had synthetic graft IVC reconstruction developed post-operative leg edema.

Pathology

Median size of the tumor was 10 cm in diameter (range, 6–30 cm; Table 2). Resection margins were negative in seven cases and microscopically positive in two cases. Histologic examination showed that the tumor was high grade in five, moderate grade in three and high/moderate grade in one case. Seven cases had evidence of tumor invading adjacent structures extraluminally.

Follow Up

Median survival from the surgery was 47 months (range, 1–181 months), and six patients were alive at the last follow-up including two patients with recurrence (Table 3). Post-operatively, one patient received adjuvant chemotherapy consisting of five cycles of cyclophosphamide, and doxorubicin therapy, and others were closely observed for recurrence.

Management of Recurrence

Out of eight patients who survived resection of the primary tumor, four were free of recurrence at the last follow-up, and four patients developed recurrence at the median of 14 months from the curative resection (range, 3–25 months). Two patients received systemic chemotherapy for the recurrence. One patient received six cycles of gemcitabine and taxol with subsequent progression, and another patient received two cycles of doxorubicin and ifosfamide and then eight cycles of doxorubicin with progression. Neither exhibited response to systemic chemotherapy.

Two patients developed local recurrence. One underwent right hemihepatectomy to resect local recurrence of segment 7 of the liver 20 months from the initial resection.

Table 2 Pathology of the IVC Leiomyosarcoma

Patient	Size (in cm)	Resection margin	Tumor grade	Extraluminal invasion
1	7.5	R0	II	Absent
2	9.0	R0	III	Present
3	10.0	R0	II/III	Present
4	12.0	R0	II	Present
5	10.0	R1	III	Present
6	22.0	R1	II	Present
7	6.0	R0	III	Present
8	30.0	R0	III	Present
9	11.5	R0	III	Absent

Table 3 Post-operative Treatment, Patterns of Recurrence and Its Management

Patient	Adjuvant Chemotherapy	Time to Recurrence (in month)	Site of Recurrence	Systemic Chemotherapy for Recurrence	Radiation for Recurrence	Surgery for Recurrence	Overall survival (in month)	Status
1	No	20	R hepatic lobe segment 7; suprahepatic IVC; lung and liver	×6 gemcitabine	No	R hepatic lobectomy; ex vivo liver resection & resection of suprahepatic IVC mass; Pulmonary wedge resections & liver RFA	73	Alive
2	No	8	Retroperitoneum, liver, lung	×2 doxorubicin & ifosfamide; x8 doxorubicin	Yes	n/a	52	Alive
3	No	25	Retroperitoneal peri-pancreatic mass	No	Yes	enucleation of the peri-pancreatic mass	47	Dead
4	No	n/a	None	n/a	n/a	n/a	155	Alive
5	No	3	R liver lobe, lung	No	No	n/a	12	Dead
6	No	n/a	None	n/a	n/a	n/a	1	Dead
7	×5 cyclophosphamide & doxorubicin	n/a	None	n/a	n/a	n/a	181	Alive
8	No	n/a	None	n/a	n/a	n/a	8	Alive
9	No	n/a	None	n/a	n/a	n/a	1	Alive

Eight months later, recurrence at the superior resection margin of the IVC was found and the patient underwent ex vivo liver resection to allow resection of the second recurrence near the remaining IVC. At 47 months from the initial surgery and following the two resections of recurrences, the patient was found to have additional lung metastases and liver metastases. He then underwent median sternotomy with pulmonary wedge resections and percutaneous radiofrequency ablation of the liver metastases. The patient went on to receive doxorubicin-based transcatheter arterial chemo-embolization for subsequent liver metastases and systemic therapy with six cycles of trabectedin on protocol. He is currently alive at 73 months from his initial operation with stable disease over the last 6 months. Another patient underwent enucleation of a recurrence at the uncinate process of the pancreas. Two patients received radiation therapy, one after resection of local recurrence, and the other for a local recurrence.

Discussion

Two thirds of patients with leiomyosarcoma of the IVC present with localized disease amenable to curative resection.[1] The International Registry established by Mingoli et al. has helped to clarify natural history of this rare tumor and to identify variables associated with long-term survival.[2] Among several prognostic indicators, surgical resection of the tumor with negative margins is the most important factor that leads to best outcome, with 5-year survival ranging from 33 to 68%.[2–8] The median survival of 47 months in our series supports the view that aggressive resection of IVC leiomyosarcoma with negative margins should be the goal of therapy for those without widespread metastases and who are acceptable operative candidates. We also report that such a resection can be performed with acceptable morbidity and mortality. However, many aspects of IVC leiomyosarcoma present unique challenges for optimal management.

Operative procedures required for tumor extirpation are frequently complex as a result of its retrohepatic location and close proximity to major branches of the IVC. For instance, involvement of the renal vein confluence by the tumor may necessitate nephrectomy, auto-transplantation of the kidney or re-attachment of the tumor-free renal vein stump to the IVC.[9] A 56% rate of nephrectomy in our series confirms the common occurrence of renal parenchymal or vascular involvement by the tumor, and it is consistent with 75% rate reported in the literature.[10] Right nephrectomy is frequently required as a result of short right renal vein stump. The left renal vein, however, can usually be ligated because of its substantial length and adequate venous return maintained by collateral vessels such as gonadal, lumbar and adrenal veins. The locally invasive nature of the tumor also can lead to involvement of other adjacent organs such as the adrenal gland and the liver and an extensive en bloc

resection may be required in an attempt to achieve tumor-free margins.

The location of the tumor in terms of upper, middle, or lower segment of the IVC is another aspect of the tumor that determines operative approach. It is also associated with prognosis as identified in the international registry by Mingoli et al.[2] The middle segment is usually approached by laparotomy and it carries best prognosis after curative resection with 48.3% 5-year survival rate whereas the lower segment tumor is associated with 5-year survival rate of 9.3%.[11] On the other hand, upper segment tumors require a thoraco-abdominal approach or combined median sternotomy and laparotomy. It is frequently inoperable, and the median survival in such cases is reported as 1 month.[11] Therefore, pre-operative determination of the segment of IVC involved by the tumor should be the first step in formulating management strategy. We have found that CT scan of chest, abdomen and pelvis with intravenous contrast was the most informative imaging study for this purpose. Echocardiogram was also useful in assessing intra-atrial extension of the tumor.

In our series, six patients had a completely occluded IVC by the tumor or thrombosis. Impaired venous return by the IVC in such circumstances leads to the development of collateral vessels, and the patency of the IVC is an important variable that guides management of the remaining IVC after tumor resection. Options for IVC reconstruction include placement of a synthetic interposition graft, primary repair, or patch repair of the IVC. The proponents of the ligation technique suggest that extensive development of the collateral vessels obviates the need for IVC reconstruction and that patients with stable renal function in the presence of complete IVC thrombosis tolerate ligation well.[8] In addition, the presence of complete thrombosis below the IVC tumor in the iliac or femoral veins makes post-operative thrombosis of the IVC graft likely as a result of poor inflow, and many consider it a contraindication to the use of graft reconstruction.[12] One must also consider the risk of pulmonary embolism if deep venous thrombosis exists pre-operatively. In support, Hollenbeck et al. noted two cases of peri-operative mortality from pulmonary embolism in the setting of pre-operative IVC thrombosis.[8] In such cases, IVC ligation may be safer.

En bloc resection of the tumor, however, may disrupt pre-existing collateral venous networks and adequacy of the collateral vessels cannot be predicted.[13–15] In addition, the main risks of IVC ligation, namely chronic venous insufficiency of the lower extremities and renal failure from venous obstruction may be ameliorated by IVC reconstruction. In support, we have found that post-operative leg edema was more common in cases where IVC ligation was performed when compared to synthetic graft IVC reconstruction (66% vs. 33%). Due to the small numbers in this study, it is difficult to conclusively state that IVC reconstruction is superior to IVC ligation, but safety and patency of the IVC graft have been documented in the literature in other types of retroperitoneal tumor resection, and it should be considered if no contraindication exists.[15,16]

In addition, post-operative renal failure in our series occurred in one patient who had IVC ligation. Huguet et al. also reported two cases where IVC ligation produced intra-operative anuria and in one case it was associated with renal failure and death.[14] Hardwigsen et al. also reported one case of oliguria after vascular clamping of the IVC and thus required IVC reconstruction.[15] One way to assess the need for IVC reconstruction is measurement of venous pressure in the IVC after clamping. Reconstruction of the IVC may be required if the pressure exceeds 30 mmHg.[7] As for the choice of the IVC graft, a Gore-Tex graft may be preferable to a Dacron graft in that it may better resist changes in intra-abdominal pressure associated with respiration.[6,13] A smaller-diameter graft may also be associated with better patency by maintaining a high rate of blood flow.[13]

Alternatively, primary repair or patch repair of the IVC after resection of the tumor can be performed in select cases.[8] However, due to the locally invasive pattern of growth as well as the tumor's propensity to extend intraluminally, simple excision of the tumor from the IVC and repair of the IVC may lead to high rates of positive margins. Therefore the majority of authors recommend segmental resection of the IVC.[7,17]

Contraindications to surgical resection include the presence of widespread metastases, involvement of major vascular structures such as celiac and superior mesenteric arteries, portal vein and superior mesenteric vein. Although it is not an absolute contraindication, invasion of the aorta by the tumor requires additional major vascular reconstructive procedures, and it should be carefully considered on pre-operative imaging studies.[9,12,18,19] The presence of Budd–Chiari syndrome portends an advanced disease in that the cause of death among the patients reported in the literature with unresectable IVC leiomyosarcoma was Budd–Chiari syndrome in two thirds of cases.[1] Therefore, involvement of the hepatic veins by the tumor is an important variable determining feasibility of curative resection, and its poor prognosis should be kept in mind before offering surgical resection. In rare circumstances, however, IVC leiomyosarcoma causing Budd–Chiari syndrome can be resected using complete hepatic vascular exclusion and re-anastomosis of the hepatic vein stump to the remaining IVC or a synthetic graft.[20]

Recurrence after curative resection of the tumor occurs in approximately 57% of patients, and about a fourth of them are local recurrence only.[2] In our series, recurrence

occurred at a median 14 months. The most common site was the liver and the lungs. Management of recurrence poses a difficult question since there is no standard approach with proven benefit. Radiation has been used in both neo-adjuvant and adjuvant settings, and some believe it may help with local control of disease.[3] Due to the large size of the tumor, however, a wide area needs to be incorporated in the radiation field, and this can be associated with significant damage to adjacent organs. Neo-adjuvant doxorubicin-based chemotherapy has also been used in a small number of patients without proven benefit.[19] Adjuvant chemotherapy based on doxorubicin or combination of doxorubicin and ifosfamide has been shown to prolong time to recurrence and overall survival in other types of sarcoma.[21,22] It may have some benefits in the treatment of IVC leiomyosarcoma, but its rarity makes it difficult to prove efficacy.

Surgical resection of local recurrence or metastasis of the IVC leiomyosarcoma has not been widely reported in the literature (Table 4). The most commonly performed procedure was local excision of retroperitoneal recurrence, followed by lung metastatectomy. We performed resection of recurrences in two patients. One patient is alive at 73 months from the initial operation and after resection of three subsequent recurrences, and the other patient died at 47 months. In view of the fact that aggressive surgical treatment has been utilized with success in some cases of recurrent or metastatic sarcoma,[30,31] surgical resection should be considered in select cases of recurrent IVC leiomyosarcoma. Admittedly, these patients who were eligible to undergo such an aggressive surgery were highly selected, and considerations should be given to other aspects of individual's disease process such as interval and pattern of tumor progression and general condition of the patient.

Conclusion

Long-term survival is possible after curative resection of IVC leiomyosarcoma. Surgical resection can be performed with acceptable morbidity and mortality. A synthetic interposition graft for reconstruction of the IVC is associated with a lower risk of lower extremity edema than IVC ligation, and it should be used in select cases. Recurrence of this rare tumor is common, and resection should be considered in light of the tumor biology and the general condition of the individual patient.

Table 4 Literature Review of IVC Leiomyosarcoma Recurrences Managed by Surgical Resection

Author	Year	Age	Gender	Site of Recurrence	Time to Recurrence	Operation	Chemotherapy	Radiation	Survival	Status
Beiles et al.[23]	1997	44	F	Local	76	Local excision & repair with ePTFE patch	No	No	23	Alive
Cope & Hunt[24]	1954	33	F	Local	16	Local excision, IVC resection, R nephrectomy	No	Yes	29	Alive
Demers et al.[19]	1992	42	F	Local	17	Local excision, transverse colectomy	Yes	Yes	23	Dead
		24	F	Local	30	Local excision, debulking	Yes	No	72	Dead
Dzsinich et al.[25]	1992	48	F	Lung, hip & femur	?	Lung lobectomy	?	?	132	Dead
		74	F	Local	?	Local excision, ePTFE graft	?	?	36	Alive
Ito et al.[4]	2007	60	F	Local	29.5	Local excision, small bowel resection	Yes	No	90.5	Dead
		48	M	Lung	26.4	Lung wedge resection	Yes	Yes	82.5	Dead
		58	F	Local	19.8	Local excision, small bowel resection	Yes	Yes	69.4	Dead
		39	F	Trunk	49.7	Local excision	Yes	Yes	73.9	Alive
Kasano et al.[26]	1995	51	F	Right atrium & local	7	Resection of R atrium tumor thrombus, local excision	No	No	12	Alive
Stuart et al.[27]	1972	58	F	Liver	16	Partial hepatic resection	No	No	35	Dead
Verela-Duran et al.[28]	1979	49	F	Lung	9	Lung wedge resection	No	No	24	Alive
Yuzer et al.[29]	2004	39	M	Local	15	Local excision & Dacron graft	Yes	Yes	?	Alive

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