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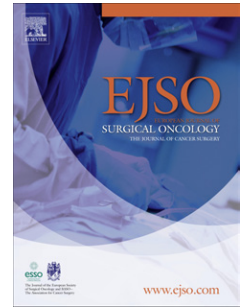
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**Oncovascular surgery**

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## Abstract

### BACKGROUND

Surgical resection remains the cornerstone for the curative treatment of oncological disease. When a tumour mass encases a critical arterial or venous structure, successful symptom relief and long-term oncological control may be achieved through careful preoperative planning within a multi-disciplinary team incorporating oncological and vascular specialists. To highlight the strategic issues pertaining to the vascular management of these patients, this review addresses the principles in planning *oncovascular* surgery, namely where cancer resection necessitates concurrent ligation or reconstruction of a major vascular structure.

### DESIGN

A multiple electronic health database search was performed, including Medline, Embase, and Scopus.

### RESULTS

The published outcomes for different malignancies suggest that survival is dependent upon complete clearance of the primary pathology and tumour biology rather than vascular-related complications.

### CONCLUSION

Major vessel involvement of a tumour mass should not necessarily be considered a barrier to *en bloc* resection and hence curative surgery. Radical surgical resection may offer the only chance for cure or palliation for these patients. Detailed preoperative planning within an extended multi-disciplinary team that includes vascular specialists is essential for these complex patients.

## INTRODUCTION

Adequate surgical clearance of neoplastic disease becomes problematic when the tumour mass encases a major vascular structure. This may be taken by some as an indicator of non-resectability. Yet, with careful pre-operative planning within a multidisciplinary team (MDT) that includes oncology and vascular specialists, favourable outcomes may be achieved through a collaborative and co-ordinated approach.

To highlight the strategic issues pertaining to the vascular management of these patients, this review addresses the principles in planning *oncovascular* surgery, namely where cancer resection necessitates concurrent ligation or reconstruction of a major vascular structure. The outcomes of oncovascular resections for a variety of cancers, principles of patient selection and strategies for the vascular management of these patients are considered along with a proposed management algorithm.

### *Search strategy*

A multiple electronic health database search was performed, including Medline, Embase, and Scopus, on all articles published up to 2010. These databases were searched using exploded Medical Subject Heading terms: ‘cancer’, ‘vascular’, ‘arterial’, and ‘venous’. Further potentially useful articles were identified through scrutiny of references.

### **Outcomes of Oncovascular Resections**

Given the small proportion of cancer patients with major vascular involvement, summative evidence is based upon case series that are heterogenous and often small. Despite the absence of high-level evidence, these reports affirm the achievability of radical surgery most notably for lower limb and retroperitoneal sarcomas, urological and pancreatic malignancies. There have been no published case series of major vascular reconstruction in patients undergoing resection of primary or recurrent gastrointestinal malignancies, which is likely to relate to the high propensity for systemic disease of these solid tumours.

A recurring inference in the published literature is that, in selected patients, radical oncovascular resections do not necessarily amplify perioperative mortality in comparison to more conservative surgery. Cancer free survival continues to be primarily related to resection margin status and tumour biology.

#### *Lower limb soft tissue sarcoma*

Approximately 3% of patients with lower limb soft tissue sarcomas present with involvement of the neurovascular bundle. Lower limb soft tissue sarcoma (FIGURE 1) excision with artery and/or vein reconstruction has been reported in small, single centre series (1) (2) (3) (4) (5). Although heterogeneity in surgical techniques impairs direct comparisons, these series report mortality rates of 0-4.8%, tumour control in 86-100% of patients and limb salvage in 92-94.1%. Post-operative oedema was observed in approximately 40% of patients with venous involvement, although there was no evident difference between those who had undergone vein ligation or reconstruction (3) (2). Morbidity arises predominantly from wound complications, with dehiscence reported in 33-57% and graft infection rates of 10-28% (1) (2) (3) (4) (5).

#### *Retroperitoneal sarcoma*

Retroperitoneal sarcomas represent approximately 15% of all soft tissue sarcomas. Resection of these tumours is challenging when they surround the aorta or inferior vena cava (IVC). The largest published series of patients undergoing concurrent aortic or IVC replacement comprises 25 cases and reported an operative mortality of 4% and 2-year and 5-year survival rates of 90% and 66.7% respectively (6). In comparison, median survival in patients who had complete macroscopic resection but positive margins on histology was 21 months, and only 8 months following debulking surgery. Successful *en bloc* resection has been described with replacement of both the aorta and IVC (7).

#### *Urological*

Retroperitoneal extension of renal cell carcinomas can become extensive due to

asymptomatic progression. Of the 4-10% with tumour thrombus, approximately a quarter require IVC resection for disease clearance. A retrospective analysis of 40 patients who required IVC intervention during nephrectomy (23 IVC ligation, 13 segmental resection and 4 filter deployment) found 2% perioperative mortality and 60% 5-year cancer specific survival in absence of nodal or metastatic disease (8). Importantly, cancer specific survival was akin to those that did not require IVC intervention.

There is limited experience of surgical resection of metastatic testicular tumours encasing the abdominal aorta, IVC or iliac systems (FIGURE 2). An early case series reported six heterogeneous patients that had undergone retroperitoneal lymphadenectomy and concomitant aortic reconstruction via a thoracoabdominal approach. There were no vascular related complications and four patients were disease-free following 4-55 months, whilst two died of metastatic disease (9). In another series by the same group, resection of metastatic germ cell tumour along with IVC ligation was performed in 19 patients along with concurrent aortic resection and bypass in two cases (10). IVC reconstruction was not attempted concomitantly in any patients; collateral venous return from the lower extremity was allowed to occur via the hypogastric veins, ascending lumbar veins and the portal system. Early complications including prolonged ileus, small bowel obstruction, wound dehiscence, and pneumonia were observed in 52% of patients. Eleven of the 19 patients survived more than 6 months with a median survival of 29 months, of whom four had persisting lower extremity oedema, three complained of chronic lower limb pain, one developed varicose veins, and one thrombophlebitis. One patient subsequently underwent IVC grafting to reduce venous hypertension, which failed due to thrombosis. An important prognostic indicator was pre-operative tumour marker levels; no patient with elevated levels prior to resection survived more than 15 months and five of the six that died of recurrent disease did not have normalization of tumour marker levels of post-operatively.

These early experiences have been replicated elsewhere. A report of six heterogeneous patients who underwent retroperitoneal adenectomy and IVC resection without replacement demonstrated no mortality or vascular related complications (11). During the follow up period there were two deaths relating to disease

progression and resolution of lower limb oedema was seen in all cases, though this took up to 14 months. Another cohort of 15 heterogeneous patients, five of whom had patent IVCs and underwent caval replacement using synthetic bypass grafts, found no perioperative mortality or vascular related complications (12). Of the patients with preoperative caval compression, 50% improved following surgery due to development of collateral vessels. These patients were managed with prophylactic doses low molecular weight heparin on the first post-operative day, followed by therapeutic doses thereafter. Patients were subsequently warfarinised with a target international normalized ratio of 2.5-3 for 2-3 months duration.

These experiences are limited by their small and heterogeneous case mix. However taken together they highlight the feasibility of IVC resection with retroperitoneal lymphadenectomy, and that post-operative morbidity is lessened through preservation of abdomino-pelvic venous collaterals.

#### *Pancreas*

Upto 80–90% of patients with pancreatic cancer will have inoperable disease at the time of diagnosis and one-third present with locally advanced, non-metastatic disease. Survival rate for patients who undergo an incomplete resection are akin to those with inoperable disease treated with chemoradiation only(13). Portal vein (PV) and superior mesenteric vein (SMV) invasion is frequent due to the intimate relationship of the pancreatic head and uncinate process to these vessels. Furthermore, venous involvement may not be fully ascertainable from preoperative imaging; in a series of 43 patients requiring pancreaticoduodenectomy with PV or SMV reconstruction, vascular involvement was not suspected from pre-operative CT or endoscopic ultrasound imaging in 20 cases (14). Encasement of the adjacent arteries and occlusion of the SMV-PV confluence are associated with irresectable disease advancement (15), although management of non-occlusive venous involvement presents a controversial challenge(16). Extending pancreaticoduodenectomy to include PV or SMV resection increases the potential for a curative resection although this is counterbalanced by the need mobilise PV or SMV from surrounding tissue and the risk of haemorrhage.



Three contemporary series detailing resection of SMV-PV segments in 143 patients have reported mortality rates between 3.5-6% (17) (18)(4). Two systematic literature reviews prior to these series have also addressed the role of synchronous PV–SMV resection during pancreatectomy(19) (20). The first comprised 1,646 heterogeneous cancers from 52 studies and found a median survival of 13 months, and 1-, 3- and 5-year survival rates of 50, 16 and 7% respectively (20). Venous resection was associated with microscopically positive resection margins in 40% and a 70% incidence of lymph node involvement. The second systematic review examined data from 399 patients with pancreatic carcinoma only from 12 studies. Mortality rates were found to range between 0-7.7%, median survival 13-22 months, and 1- and 5-year survival of 31-83% and 9%-18% respectively (19). Together, these data suggest that survival results for pancreatectomy combined with PV or SMV resection do not significantly differ from procedures without venous involvement. The mid- and long-term survival in these series suggests that vascular resection can be pursued when the opportunity to obtain negative microscopic margins is possible and that nodal involvement and metastases limits prospect for cure(21).

### **Patient selection**

Patient selection for surgery is initially carried out the disease-specific MDT and follows local and systemic staging. Management is individualised to the patient with expectation that disease-free survival or symptom control will justify surgical risk. The decision to operate and surgical strategy thus follows liaison between the disease-specific MDT and vascular surgeon and is guided by tumour staging, assessment of patient risk factors, and a longer-term oncological management strategy. Operative considerations are highlighted below and are individualized to the patient depending extent of vascular involvement.

Regional tumour recurrence without evidence of metastases on re-staging imaging may be appropriate for radical resection. Obliteration of normal tissue planes from previous dissection can make proximal and distal vessel control challenging. Radical resection of metachronous disease with vascular involvement is inadvisable if clearance cannot be expected on the basis of pre-operative imaging or further recurrence is likely. In such circumstances, less radical cytoreduction or non-surgical

management should be considered.

Preoperative cardio-respiratory assessment should be carried out according to the standard principles of major arterial surgery, particularly if there is involvement of the aorta or vena cava or when surgery involves thoracic access (22, 23). Cardiac disease, diabetes mellitus, renal insufficiency and malnutrition all confer higher perioperative risks. In such patients, pre-operative assessment by a senior anaesthetist can stratify risk. In addition, cardiopulmonary exercise testing is gaining popularity to identify patients with compromised physiological reserve and guide preoperative optimisation (24) (25). Informed consent should involve detailed discussion of both oncological and vascular procedures and the comparative outcomes of radical and conservative resections.

### **Imaging**

Alongside cross-sectional staging, imaging of the arterial and venous systems is required to assess the extent of vascular involvement, plan surgical access for vessel control, the extent of *en bloc* resection and requirement for revascularisation. Contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) have superseded catheter angiography and generally suffice for both purposes (26) (27). MRI in particular has utility in delineating tissue planes and is able to interrogate extent of vascular invasion. A prospective evaluation of MRI in the evaluation of vascular invasion by bone and soft-tissue tumours on the basis of findings of partial or total encasement found 64% sensitivity, 95% specificity, 88% positive predictive value and 83% negative predictive value (28). Conversely detection of vascular invasion on the basis of the findings of a stenosis by contrast enhanced MR angiography found 82% sensitivity, 85% specificity, 75% positive predictive value and 90% negative predictive value. By comparison, a smaller retrospective analysis of CT angiography showed 100% sensitivity, 80% specificity, 62.5% positive predictive value and 100% negative predictive value.(29).

Colour-flow 'duplex' imaging allows real-time visualisation and haemodynamic assessment of vessels by a combination of grey-scale (B-mode) and pulsed-wave

Doppler ultrasound. B-mode imaging provides anatomical detail, including diameter and presence of plaque or thrombus. Colour-flow Doppler quantifies blood flow and allows identification of increased blood velocity by a change in colour within the lumen of the artery. By combining these two modalities, occlusion and stenosis can be quantified. Though non-invasive and inexpensive, Duplex is operator-dependent and difficulties may arise with deep or tortuous arteries where signal return is reduced and optimum angles of insonation are difficult to obtain. In expert hands Duplex arterial assessment of the aorto-iliac region has been demonstrated to have a sensitivity and specificity of 89% and 90% (30), and from the common femoral to the distal popliteal artery a sensitivity and specificity of 84–87% and 92–98% in comparison to catheter angiography (31). Intravascular ultrasound may be considered as a complementary diagnostic modality to determine vessel wall invasion. However, this is invasive and experience of its use in the peripheral arterial system is limited (32) (33).

### **Operative considerations**

Oncovascular MDT planning should address operative considerations, including: access to the surgical field, proximal and distal vascular control, need for endovascular adjuncts and strategies for arterial/venous reconstruction. An algorithm summarising the main surgical strategies is presented in FIGURE 4 and described below. Resection by ‘shaving’ a tumour mass off the surface of an adjacent vessel avoids the morbidity associated with vessel ligation or reconstruction. This is counterbalanced by the risk of leaving tumour deposit on the vessel adventitia or delayed vessel rupture if there is excessive dissection in the subadventitial plane.

The MDT should also consider the nature of the operative field. For gastrointestinal resections, soft tissue coverage of any anastomosis or prosthetic bypass graft is recommended to avoid the risk of arterio-enteric fistula(34). Preoperative radiotherapy to the surgical field may result in radiation arteritis that may compromise revascularisation or require more distal vessel exposure. Furthermore, attenuated vascularity and poor wound healing increase risk of infection and anastomotic dehiscence(35).

It should additionally be appreciated that radical tumour resection encompassing extensive perivascular tissue may cause destruction of regional lymphatics. This may result in chylous ascites if there has been extensive retroperitoneal dissection, requiring drainage. Acute lymphatic leak can be a serious if uncommon hazard following extensive cervical dissection, resulting in acute laryngeal oedema and airway compromise (36).

#### *Endovascular adjunctive procedures*

Interventional radiology techniques may be applied as adjunctive procedures prior to or during resection of inaccessible or vascular tumours, and their utility should be considered as part of the planning MDT. Embolisation may be performed to prevent haemorrhage from hostile surgical fields (37). Typically metal coils, glues or particulate agents are deployed via catheter into a feeding vessel to act as a nidus for thrombosis. This is most commonly carried preoperatively in the angiography suite but may be performed in the operating theatre if imaging facilities are available. The principal complication of embolisation is inadvertent maldeployment into a main trunk vessel to cause distal ischaemia. Intraoperative bleeding may be controlled by embolisation or intraluminal balloon occlusion catheters, which are positioned using fluoroscopic guidance and removed at the end of surgery. This latter technique should be performed with care to avoid iatrogenic vessel injury or thrombosis.

Vena cava filters are placed to protect against the long-term development of pulmonary embolism in patients with deep vein thrombosis. This is counterbalanced by an increased risk of complications that include ilio caval thrombosis in up to 10%, access site thrombosis, vessel erosion, migration and fracture. Furthermore, maldeployment in relation to the renal veins may lead to renal failure. Caval filters may be considered prior to oncovascular surgery in the presence of a proximal DVT, particularly if there is a history of pulmonary emboli, intolerance to anticoagulation or the patient is regarded as high risk for thromboembolic complications. IVC filters are additionally of benefit in patients where caval invasion by tumour has been detected during preoperative staging (8). Temporary protection can be provided by retrievable caval filters, which may be removed after 30 days to avoid long-term sequelae.

Another facility provided by interventional radiology is in the context of radical neck dissection where there is involvement of the carotid arteries. Catheter angiography to visualize cerebral circulation may be combined with internal carotid artery occlusion balloon testing - the modified Matas test. Response to internal carotid occlusion is determined clinically and electroencephalographically, and may be done with low morbidity in the absence of atherosclerotic disease (38). Tolerance to controlled balloon occlusion of the internal carotid artery would support ligation if sacrifice of this artery were to be required.

#### *Strategies for Arterial Reconstruction*

Arterial reconstruction following *en bloc* tumour resection follows established operative principles whereby a local defect may be repaired using a patch or an excised segment bridged using a bypass graft (FIGURE 5). In selected cases, ischaemic injury can be reduced by utilization of a shunt to maintain distal perfusion (39). Arterial reconstruction following tumour resections are associated with patency rates akin to those for atherosclerotic disease; in a series of patients with retroperitoneal sarcomas involving the aortoiliac segment, graft patency rates of 89% were achieved following reconstruction with synthetic grafts after a median 19.3 months of follow up (6). Arterial replacement during lower limb sarcoma excisions has been described with primary and secondary (assisted) 2-year patency rates of 58.3% and 78.3% respectively, which was unchanged at 5-years (1).

For bypass surgery, either autologous vein or synthetic grafts may be used. Venous conduits are in general preferable over prosthetic in view of resistance to thrombosis, infection and late anastomotic stenosis. Four-year patency rates of 49% and 12% for infrainguinal bypasses extending below the knee joint using vein and prosthetic grafts respectively have been described (40). Long saphenous vein (LSV) is the most commonly used conduit on account of its accessibility and length. An alternative to replace large diameter vessels is the femoral vein, which may be harvested below the confluence with the deep femoral with low morbidity and leg swelling, to replace large diameter vessels (7, 41-43). Use of splenic, jugular and left renal veins have also been described, and may be appropriate if in the same surgical field as the cancer resection.

Conventionally used prosthetic conduits include polyethylene terephthalate (Dacron) or expanded polytetrafluoroethylene (ePTFE). Use of non-conventional conduits may also be considered, an example being autologous superficial femoral artery with the harvested femoral segment bridged with a synthetic graft (44). Irrespective of graft material, postoperative antiplatelet medication is required to prevent thrombosis.

#### *Strategies for Venous Reconstruction*

Venous resection may be required if tumour is adherent to or encompassing the vessel. Veins that are chronically occluded or those in the peripheries may be sacrificed without reconstruction with minimal morbidity; less than a third of patients undergoing resection of occluded IVCs as part of oncological resection suffer long-term lower limb oedema(10). In contrast, ligation of a patent major vein is likely to cause significant morbidity from thromboembolism or venous hypertension due to inadequate collaterals. A series of IVC ligations to prevent emboli showed that half of patients suffered long-term peripheral oedema and venous hypertension (45).

Accordingly, vein reconstruction may be considered as unnecessary if preoperative imaging demonstrates significant collateralisation or there is pre-existing occlusion and that tumour excision is not expected to injure venous collaterals. Pre-operative planning should consider whether there is radiological evidence of venous occlusion, the extent of collateral vessel development and clinical evidence of peripheral oedema. Venous bypass therefore should be considered only if there is expected to be inadequate venous return through collateral vessels and, if performed, close follow up with serial duplex scanning is advisable although there is no evidence on optimal frequency of scans.

It has been suggested that involvement of less than half the circumference of a vein may be managed by either primary closure or venous patch repair. Conversely vessel resection is indicated for lesions involving greater than half the circumference (6). Veins may be patched or bypassed in a manner akin to arteries, although the long-term outcomes are less predictable or assured. This is primarily due to an amplified risk of thrombosis from slow blood flow and competitive flow through developed

collateral vessels. Accordingly, reconstruction typically relies upon use of autologous conduits and short-term anticoagulation postoperatively which is followed by long-term antiplatelet therapy. The use of adjunctive arterio-venous fistulae may be considered to address low flow and pressure states within the deep veins on an individualized basis.

Reconstruction of the IVC-iliac vein segment has been performed with limited but acceptable mid-term outcomes. Reported inpatient mortality and graft failure rates are 6.9-8.7% and 8.3-12.5% respectively (6, 49, 50). A series of 42 patients undergoing IVC replacements showed an overall 62% 3-year patency (46). In absence of autologous conduit, caval replacement using cryopreserved aortic homograft (47) bovine pericardium (48) and ePTFE have also been described. The most widespread iliac vein reconstruction is the Palma procedure, where contralateral LSV is mobilized to construct a cross femoral veno-venous graft to blood to bypass a common iliac occlusion. This is associated with 4-year patency rates of up to 83%, comparing favourably with conventional vein bypass (51). Reconstruction of lower extremity veins has a more variable reported outcome, with midterm patency rates varying between of 33-79.3% (2) (1, 4). Experience with patients undergoing lower limb sarcoma excision has shown modest improvement in peripheral oedema with venous reconstruction over ligation alone (1).

## **Conclusion**

Major vessel involvement of a tumour mass should not necessarily be considered a barrier to *en bloc* resection and hence curative surgery. Indeed, aggressive surgical management may offer the only chance for cure or palliation for these patients. The published outcomes for a variety of malignancies suggest that survival is dependent upon complete clearance of the primary pathology and tumour biology rather than vascular-related complications. Detailed preoperative planning within an extended multi-disciplinary team that includes vascular specialists is essential for these complex patients.

## FIGURE LEGENDS:

## FIGURE 1:

CT (a) and MRI (b) scanning of a high-grade sarcoma in the right femoral triangle. Intraoperative image (c) showing dissection plane between common femoral artery and sarcoma following extraperitoneal control of the external iliac artery. Image (d) shows final specimen resected en bloc with common/superficial femoral vein with clear tumour margins.

## FIGURE 2:

MRI scanning of a large teratoma (arrowed) involving the right iliac arterial and venous systems. Resection entailed preoperative internal iliac artery embolisation, retroperitoneal approach to allow control of infrarenal aortic and posterior access to the tumour mass. Resection was performed with en bloc resection of the external iliac vein and adventitial stripping of the external and internal iliac arteries.

## FIGURE 3:

CT image (Fig 4a) showing local recurrence of a colon adenocarcinoma (arrowed) following a prior right hemicolectomy, with no metastatic disease. The tumour was encircling the right external iliac artery. Following ureteric stenting and *en bloc* resection of the tumour mass was performed including the previous ileo-colic anastomosis, adherent small bowel and involved external iliac artery. The external iliac veins were not involved and the artery was replaced with a LSV interposition graft. The patient remains well with no evidence of recurrence and no vascular graft complications at 3 years (Fig 4b).

## FIGURE 4:

Algorithm for management of vascular structures involved during radical tumour resection.

## FIGURE 5:

Fig 5a: Aortic replacement using a Dacron tube graft following resection of a recurrent teratoma encasing the aorta. Fig 5b: Resected specimen including the aorta (highlighted with probe).



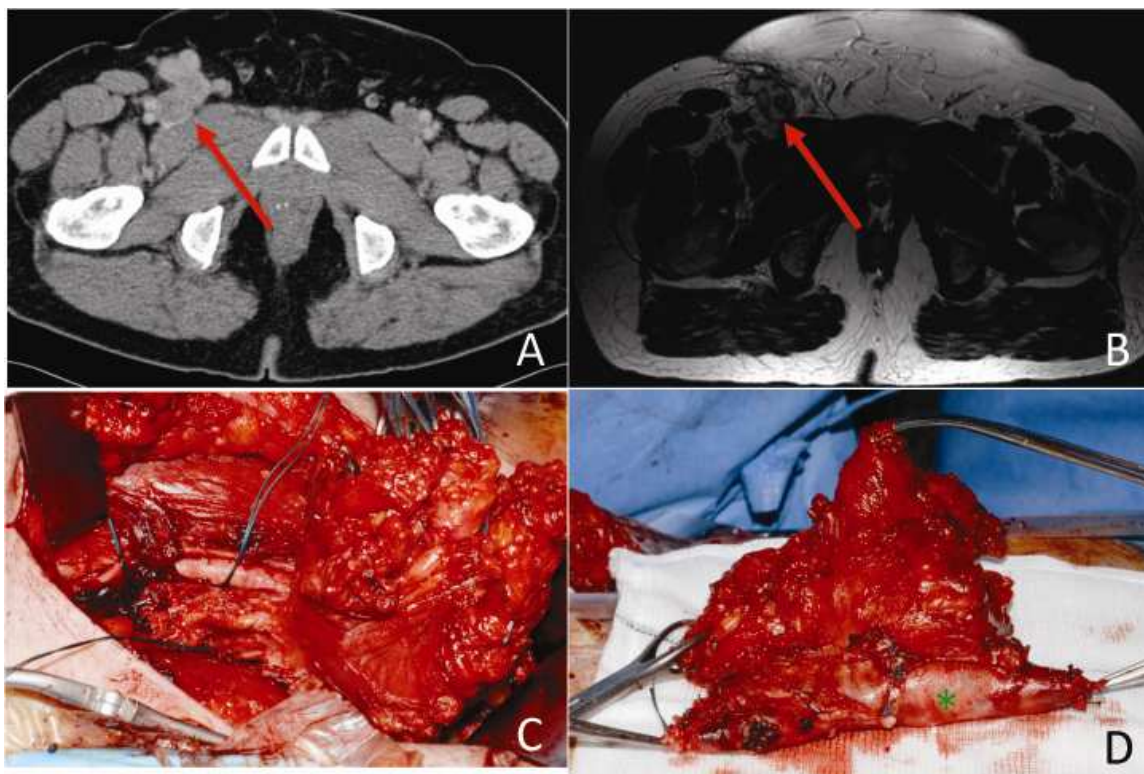
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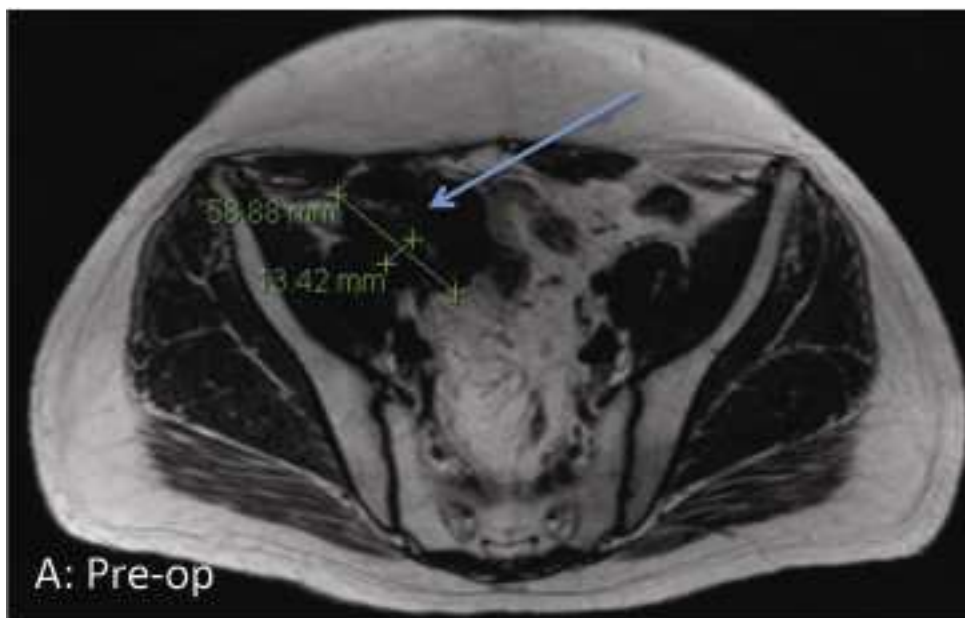
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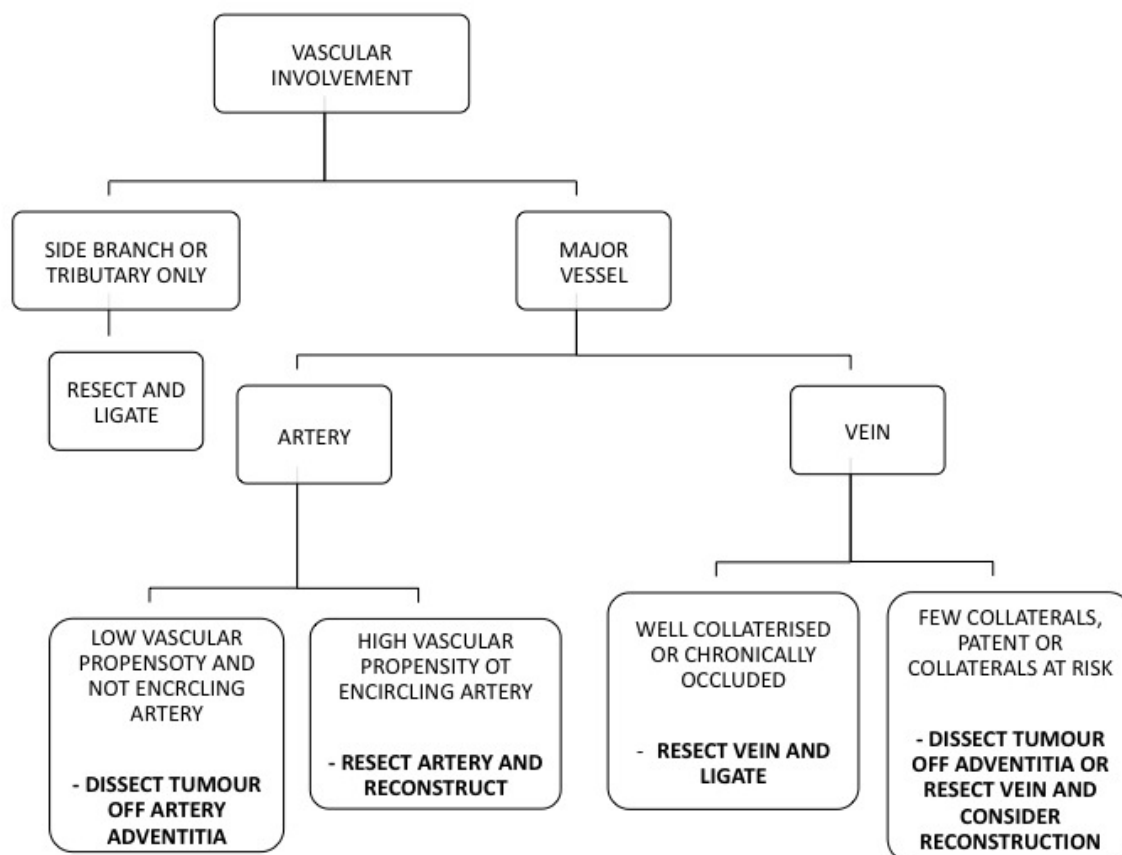
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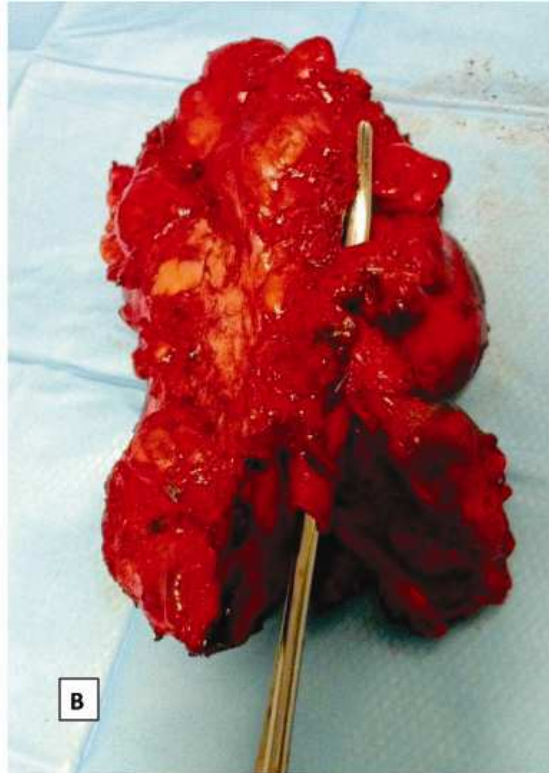
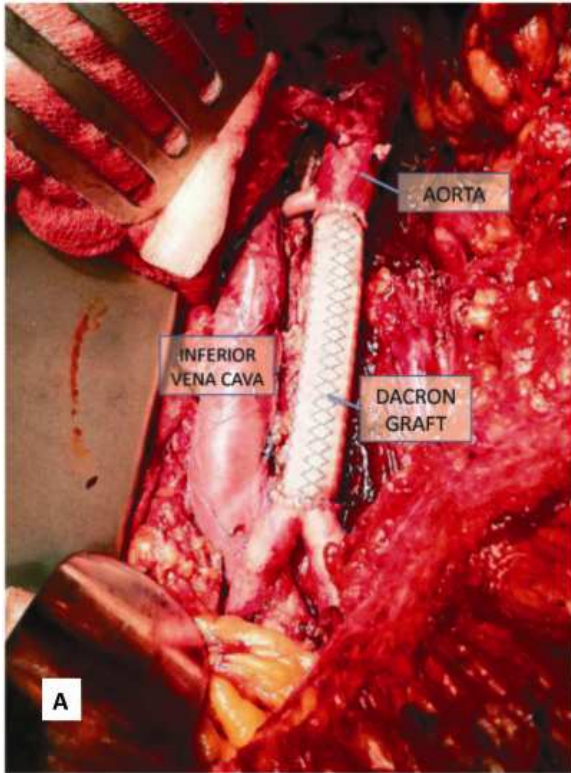
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