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Surgical treatment of acute limb iscahemia in the presence of malignancy

Gareth Morris-Stiff*, Michael H. Lewis

Department of Surgery, Royal Glamorgan Hospital, Ynysmaerdy, LLantrisant, Rhondda Cynon Taf, CF72 8XR, United Kingdom

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ABSTRACT

Objectives: The aim of this study was to examine the outcome of surgical treatment of acute limb ischaemia (ALI) developing in the presence of malignancy.
Methods: Patients undergoing emergency surgery were identified from theatre registers, notes were reviewed, and data collected in relation to indications for, and outcome following operation. All patients with a current or past medical history of histologically confirmed malignant disease were identified and their notes specifically reviewed to determine the staging of their tumours. The results of the malignancy cohort were compared to a group of patients undergoing surgery for ALI of other aetiologies.
Results: Fourteen patients with a malignancy were identified with ALI and in addition there were 102 without malignancy. The cohort with a malignancy contained a higher proportion of males ($p = 0.0305$), and a greater number of smokers ($p = 0.037$) than those with other aetiologies for ALI. The peri-operative management of the 2 groups was similar. Histological examination revealed tumour thrombus in only 1 case. The recurrence (29% *versus* 18%; $p = 0.328$) and amputation rates (29% *versus* 17%; $p = 0.278$) were similar, however, the 30-day (50% *versus* 30%; $p = 0.038$) and 60-day mortality rates (100% *versus* 35%; $p < 0.001$) were significantly higher in the malignancy group.
Conclusions: The development of ALI in patients with malignant disease may be regarded as a terminal event despite comparable performance status at the time of surgery to those with other cause for ALI. The role of surgery in patients with known advanced malignancies appears to be of dubious benefit with little survival benefit.

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1. Introduction

The link between thrombosis and malignancy was first documented by Armand Trousseau in 1865 when he reported that unexpected migratory thrombophlebitis may be an indicator of an occult visceral malignancy, the so called Trousseau syndrome.[1] The definition was expanded by Sack et al. [2] and it now includes patients with known malignancies who develop thromboses in arterial or venous systems. The condition has a complex multifactorial aetiology reviewed extensively by Varki.[3]

When a patient attends with an ALI, it is imperative to proceed urgently to attempt revascularisation so as to maximise the chances of limb salvage. In this setting, there may be little opportunity to screen for tumours but if a history of active malignancy is reported then this may influence the subsequent management.

There is currently little data relating to the management of an ALI in patients with concurrent malignant disease. The aim of this study was to compare the outcomes of surgery for ALI in patients with an active malignancy and those with other aetiologies.

2. Patients and methods

All patients undergoing emergency arterial surgery for ALI during the period 1993 to 2003 were identified from the prospectively maintained theatre register. Only patients in whom an embolectomy was attempted on a native artery were included and those who had occluded vascular graft were excluded. The case notes were assessed and data retrieved in relation to: demographic features, patient history and risk factors for limb ischaemia; investigations; peri-operative management; and outcome including postoperative complications. In addition a history of past or concurrent malignancy was sought through review of notes and both radiology and pathology department computerised databases, these patients being identified as a subgroup. For this group, the tumour origin, histological type and stage were recorded. The malignancy group was compared to the remainder of the cohort undergoing surgery for ALI.

Comparison of proportions was by the Chi-squared test and categorical data by means of the Student's t test with statistical significance taken at the 5% level.

* Corresponding author. 1 Golygfa'r Eglwys, Maesycoed, Pontypridd, Rhondda Cynon Taf, CF37 1JL, Wales, United Kingdom. Tel.: +44 1443 650625.
E-mail address: garethmorrisstiff@hotmail.com (G. Morris-Stiff).

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Table 1
Comparison of the demographic details of patients with malignancy and atrial fibrillation as the aetiological factors for acute limb ischaemia.

	Malignancy	Other	Significance
Age ± SEM (range)	71.5 ± 8 (47–83)	72.9 ± 13 (43–99)	$p = 0.684$
Gender – M:F	9:5	35:67	$p = 0.037$
ASA score (%) – 2:3:4	43:36:21	41:52:9	$p = 0.287$
History of smoking	64%	37%	$p = 0.037$

ASA = American Society of Anesthesiologists.

3. Results

During the interval covered by the study, 116 patients underwent emergency vascular surgery for ALI of which 14 (12%) had or were subsequently diagnosed with a malignancy.

The underlying malignancies were bronchial adenocarcinoma ($n = 4$); transitional cell carcinoma bladder ($n = 2$); lymphoma ($n = 2$); oesophageal adenocarcinoma ($n = 2$); bronchial squamous cell carcinoma ($n = 1$); colonic adenocarcinoma ($n = 1$); pancreatic adenocarcinoma ($n = 1$); gastric adenocarcinoma ($n = 1$); vulval squamous cell carcinoma ($n = 1$); and chronic lymphatic leukaemia ($n = 1$). In 4 cases, patients had known malignancies, and in 10 cases tumours were diagnosed at the time of admission with ALI following surgery or shortly thereafter.

The demographic features are summarised in Table 1. Patients with malignancies were predominantly males ($p = 0.030$). The mean age and distribution of patients according to ASA grade was comparable in the 2 groups. However, the proportion of smokers was significantly higher in the malignancy group ($p = 0.037$).

The peri-operative management of the 2 groups is summarised in Table 2. The delay from first presentation to surgery was similar for the 2 groups. All aspects of investigation and management were comparable for the 2 study groups including use of preoperative imaging, preoperative heparinisation and antibiotic use. Imaging studies were performed in 9 of 14 patients in the malignancy group pre-operatively and a further 2 patients underwent intra-operative angiography. Only 1 patient had significant arterial disease and underwent a concurrent bypass procedure. In the non-malignancy ALI group, 10 patients had underlying vascular disease which was felt to be contributory to the ALI and underwent bypass surgery.

Histological examination of specimens removed from patients with a malignancy identified carcinoma cells in 1 patient with a colonic adenocarcinoma.

The outcomes of surgery are summarised in Table 3. The overall complication rates were comparable in the 2 groups. The rates of recurrent emboli for patients with malignancy were higher than for those with other causes of ALI but not significantly so (29% *versus* 18%; $p = 0.328$). The requirement for subsequent amputation was also higher but again not significantly so (29% *versus* 17%; $p = 0.278$).

The 30-day mortality rate was significantly higher in the malignancy group (50% *versus* 30%; $p = 0.038$). When the period of assessment was extended to 60 days, all those with a malignancy had died and the difference was more significant (100% *versus* 35%; $p < 0.001$).

4. Discussion

The primary finding of this observational study is that patients with malignant disease undergoing emergency surgery for ALI have a significantly poorer outcome than other patients with ALI undergoing surgery who were of similar age and comorbid status. This was manifested in terms of a higher rate of a higher post-operative mortality rate both at 30 and 60 days.

Table 2
Peri-operative investigation and management.

Perioperative Factors	Malignancy $n = 14$	Other $n = 102$	Significance
Preoperative imaging (%)	64	44	$p = 0.156$
Preoperative heparinization (%)	86	79	$p = 0.579$
Prophylactic antibiotics (%)	57	61	$p = 0.196$
Local anaesthesia (%)	43	41	$p = 0.849$
Bypass surgery performed (%)	7	10	$p = 0.750$
Median delay prior to embolectomy	17 hr	23 hr	$p = 0.953$

There are two potential causes of ALI in patients with malignancy. Likely to be the most common and probably under-documented is in relation to a paraneoplastic syndrome, however, case series of embolectomy rarely mention this aetiology. The occurrence of ALI in acute myeloid leukaemia has been well-documented.[4] A detailed review of the literature identified only two case series specifically assessing emboli arising in patients with malignancy.[5,6] Rigdon reported 3 patients with malignancy-related hypercoagulability related to tumours of the breast, lung and pancreas.[5] El Sakka and colleagues reviewed all patients with critical limb ischaemia reporting to their unit of an 18-month period and found occult malignancies in 10 of 62 (16%) of those presenting acutely and 12 of 130 (9.2%) of patients with chronic symptoms.[6] They also reported 50% mortality at 6 months for those with a malignancy compared to 20.6% in those with no tumour present.

The second source of emboli is from the tumour itself and whilst numerically an uncommon cause of ALI, its novel nature makes it the subject of a greater body of literature with numerous case reports. The commonest source of tumour emboli is left-sided atrial myxomass and in 20% presentation is with symptoms related to distal embolisation.[7] Morasch and Shanik noted 20 case reports/series containing a total of 70 patients with non-myxomatous tumour emboli in addition to their own case in their literature review in 2003.[8] However, in a collective assessment of over 1500 embolectomies only 6 cases of tumour emboli were identified.[9–11] In this series, only 1 patient had malignant tissue identified on histological examination of the embolic material.

In the current series it is presumed that the occlusions were due to thrombosis occurring as part of a paraneoplastic syndrome as only 1 patient had significant vascular disease in the vessel segment containing the occlusion. The origin of the adenocarcinoma cells in the patient in whom these were identified is unclear as these would have expected to have traversed the portal system to the liver and not be present in the systemic circulation.

Despite the small volume of papers discussing the risks of arterial embolism in malignancy, there is a large volume of literature in relation to venous thrombosis developing in the presence of neoplastic disease. Although the precise mechanism is uncertain, and probably multifactorial, it is commonly said to be related to a paraneoplastic syndrome.[3,12] There is an overall increased risk for venous thrombosis in the order of 4-fold in patients with malignant disease, increasing to 6-fold in patients receiving chemotherapy.[13]

Table 3
Outcome following embolectomy.

Postoperative Complications	Malignancy $n = 14$	Other $n = 102$	Significance
Complications (%)	64	61	$p = 0.855$
Recurrence (%)	29	18	$p = 0.328$
Amputation (%)	29	17	$p = 0.278$
30-day mortality (%)	50	30	$p = 0.143$
60-day mortality (%)	100	35	$p < 0.001$

Specific tumour types said to be at higher risk of thrombosis include adenocarcinomas of the lung, stomach and pancreas[14] although increased risk has also been documented for tumours prostate, colon, brain, breast and ovary.[15,16]

In the current series, 4 of the patients were known to have malignant tumour at the time of presentation with an ALI and the remainder was diagnosed following the embolectomy, in a Trousseau-type presentation.

The management of malignancy-related thrombo-embolic disease, in addition to removal of the embolus itself and treatment of the underlying neoplasm, should include treatment with heparin as there is evidence that this may exert anti-tumour effect in addition to an anti-thrombotic effect.[17,18,19] In this series, 86% of patients eventually diagnosed with malignant disease had been heparinised preoperatively and all received post-embolectomy heparin therapy.

Limitations of the current study include the fact that given the nature of the study, there was no quality of life assessment and thus it may be argued that an operation may have benefited the patient in terms of pain relief. However, given the significant recurrence rates, amputations and subsequent mortality any benefit would be short term. A further limitation in terms of defining the extent of the problem was that data were only available on those undergoing surgery and thus the number of patients unfit and not referred for surgical assessment.

5. Conclusions

The performance of emergency vascular surgery for patients with advanced malignant disease would appear to be of limited benefit. Indeed, in cases where patients are known to have metastatic disease at the time of presentation with ALI, it may be advocated that operative intervention is not undertaken as it is clear that the perioperative mortality and subsequent survival are poor. In patients with ALI in whom no specific aetiological factor is identified, a diagnosis of underlying malignancy should be considered.

Conflict of interest

Neither author reports any conflict of interest.

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Ethical approval

Ethical approval was not sought for this observational study as gabapentin was on the hospital formulary and was widely used by the hospital pain team for resistant chronic pain of other aetiologies.

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