Introduction

The development of aorto-enteric fistulas following irradiation therapy has been infrequently recognised [1]. This report describes two patients with unresectable exocrine pancreatic adenocarcinoma who were treated initially by bypass surgery and intra-operative electron-beam therapy within the past decade, then developed vascular-enteric fistulas that could not be controlled by embolisation. The dilemma as to how vigorously to treat the resulting haemorrhage is compounded by observation of somewhat similar patients with pancreatic cancer who developed massive upper gastro-intestinal haemorrhage from benign ulcers.

Case reports

Case no. 1

A patient was readmitted to hospital with coffee-ground vomitus and melaena. Eleven months earlier, carcinoma of the exocrine pancreas obstructing both the duct of Wirsung and the common bile duct had been identified. The tumour in the head of the pancreas had been deemed unresectable because of extensive venous invasion. Treatment consisted of biopsy, antrectomy, biliary and duodenal bypass and intra-operative radiation, followed by postoperative irradiation (dosage shown in Table 1). Therapy with 5-fluorouracil was utilised initially, but was not being administered at the time of bleeding. The haemoglobin level was 6.2 g/dl on admission, and there was no indication of a coagulopathy.

As the patient underwent rapid resuscitation, including blood transfusion, he continued to bleed briskly. Emergency angiography demonstrated a bleeding point from a branch of the superior mesenteric artery. Embolisation with multiple wire coils failed to control the haemorrhage; the coils could be seen to pass through the artery into the intestinal lumen. Replacement therapy was inadequate and the patient died.

Autopsy demonstrated a large ulcer in the duodenal loop, adjacent to the head of the pancreas, which contained predominantly necrotic material with foci of malignant tissue. Within this ulcer a disrupted branch of the superior mesenteric artery was found. A small wire coil in the duodenum lay adjacent to the arterial erosion.

Case reports

Vascular-enteric fistulas associated with radiation therapy in patients with pancreatic adenocarcinoma

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Background

Irradiation therapy is being evaluated widely as an adjunct to therapy of resectable and unresectable pancreatic exocrine carcinoma. Exsanguinating haemorrhage has been an occasional late complication.

Case outlines

Two patients with unresectable cancer of the pancreas were treated by bypass, chemotherapy and both intra-operative and postoperative irradiation. Both patients died 5–11 months later of gastroduodenal haemorrhage from arterio-enteric fistulas, which were confirmed by autopsy but had been uncontrolled by selective embolisation. A third patient, for whom little other information was available, died of upper abdominal haemorrhage 5 months after a ‘curative’ resection combined with intra-operative and postoperative irradiation.

Discussion

Judgement in management is difficult because of the poor prognosis from the underlying disease on the one hand versus the fact that site of bleeding has sometimes been from complicating benign disease. Better endovascular techniques of control of such haemorrhage may be developing.

Keywords
pancreatic cancer, radiation therapy, gastrointestinal haemorrhage, embolisation therapy.
Case no. 2
An outpatient was seen following an episode of haematemesis and melaena. Five months earlier, he had presented with back pain leading to a diagnosis of carcinoma of the pancreatic head and body. Exploratory laparotomy with biopsy demonstrated extensive vascular invasion of the superior mesenteric vessels as well as the coeliac plexus. Intra-operative irradiation was combined with antrectomy, and biliary and duodenal bypass (Table 1). At readmission the prothrombin time was 16 s (normal, 11.8–14 s), the partial thromboplastin time was >50 s (normal, 25–35 s) and the haemoglobin level was 7 g/dl. The patient was resuscitated with intravenous fluids, and emergency arteriography revealed a bleeding arterial branch of what appeared to be the splenic artery (Figure 1). The splenic artery was repeatedly embolised with Gelfoam. This manoeuvre stopped the bleeding, but 2 h later in the intensive care unit rebleeding again became evident. Further transfusion and intravenous pitressin therapy were unsuccessful, death resulting within the day of admission.

Post-mortem examination demonstrated a 2.1-cm ulcer of the posterior gastric wall with an opening into the splenic artery. No embolus remained in the bleeding artery, nor was one observed in the stomach, but vomiting and diarrhoea after rebleeding would presumably have removed an embolus from the alimentary tract. Adjacent to the ulcer, the head of the pancreas showed a firm exocrine pancreatic adenocarcinoma involving the coeliac lymph nodes and extending to the ulcer but (as with the first patient) histological invasion of the artery per se was not demonstrated.

Discussion
A third patient, not included above because of incomplete information, presented with massive gastro-intestinal haemorrhage, including haematemesis, and died of rapid exsanguination at the start of resuscitation. She had undergone a "curative" resection of a carcinoma of the head of the pancreas approximately 5 months earlier and had received intra-operative and postoperative radiation. As autopsy was not permitted, her point of haemorrhage, presumed to have been from aorta to duodenum, cannot be documented, but clearly there is a need for effective plans of management in patients with this complication. In a career as a pancreatic surgeon, these three patients have been the only ones of any severity recognised with this problem by the senior author.

Various reasons have been given for upper gastro-intestinal haemorrhage related to radiotherapy of pancreatic adenocarcinoma [2–6]. Van Dam [7] found that it usually emanated from superficial capillaries and not from discrete or diffuse ulceration. Other reports noted the haemorrhage to be from a variety of vascular-digestive fistulas, such as duodeno-caval, aortoduodenal and other arterio-enteric fistulae [1,2,8,9]. De Villa et al. [9] proposed that the pathogenesis of development of arterio-enteric fistulae secondary to radiation injury is vascular damage resulting in arterial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Age and sex</td>
<td>69 years, male</td>
<td>61 years, male</td>
</tr>
<tr>
<td>Extent and location of tumour</td>
<td>5 cm from ampulla of Vater</td>
<td>6.5 cm from ampulla</td>
</tr>
<tr>
<td>Therapy</td>
<td>Antrectomy, Roux-en-Y gastrojejunostomy, choledochojejunostomy, enteroenterostomy</td>
<td>Antrectomy, cholecystectomy, Roux-en-Y gastrojejunostomy, choledochojejunostomy</td>
</tr>
<tr>
<td>IOEBRT</td>
<td>25 Gy</td>
<td>20 Gy</td>
</tr>
<tr>
<td>EBRT</td>
<td>50.4 Gy</td>
<td>50.4 Gy</td>
</tr>
<tr>
<td>Delay before bleeding</td>
<td>11 months</td>
<td>5 months</td>
</tr>
<tr>
<td>Amount of transfusion</td>
<td>13 units of packed red cells</td>
<td>11 units of packed red cells, 6 units of fresh plasma</td>
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<tr>
<td>Treatment</td>
<td>Embolisation</td>
<td>Embolisation, intravenous pitressin</td>
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<tr>
<td>Findings</td>
<td>Branch of superior mesenteric artery-duodenal fistula</td>
<td>Splenic artery-gastric fistula</td>
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IOEBRT = intra-operative electron-beam radiation therapy; EBRT = external beam radiation therapy.
pseudo-aneurysms that erode a contiguous visceral wall. Neither of our patients demonstrated an aneurysm or other lesions pathognomonic of post-irradiation arterial damage.

Clinical presentations of gastro-intestinal haemorrhage associated with radiotherapy are similar to other forms of gastro-intestinal bleeding. Because the interval between therapy and the episode of haemorrhage is usually between 4 and 21 months [4,5] and other causes of haemorrhage may intervene, such as peptic ulcer or segmental portal hypertension [10], the diagnosis of vascular-enteric fistula is infrequently considered. This possibility presents a serious dilemma, particularly in the patients whose cancer has been resected.

Radiological evaluation of late radiation injury to the bowel frequently reveals nonspecific change [11]. Endoscopy may reveal a pale gastro-intestinal mucosa with superficial telangiectasia or erosions [7], but it may be impossible to localise the source of massive haemorrhage [9]. Selective angiography in such instances is essential for its definition. In each of our patients it confirmed the exact bleeding site and also offered the option of therapeutic embolisation.

In patients with duodenal haemorrhage due to post-irradiation ischaemic necrosis of the mucosa on the medial duodenal wall, the bleeding episodes have usually proved self-limiting [6]. However, most radiation-induced gastro-intestinal haemorrhages are refractory and carry a poor prognosis. Endoscopic laser coagulation and bipolar electrocautery have provided temporary haemostasis in treatment of mucosal haemorrhages [3,4], but a high incidence of recurrent bleeding casts doubt on their long-term efficacy [4]; these measures would have little or no role to play in controlling arterial haemorrhage of such magnitude. Severe bleeding should suggest the possibility of a vascular-enteric fistula. Hirakata and colleagues [12] reported successful control of massive intestinal haemorrhage by transcatheter arterial embolisation in a patient with irradiation for cervical cancer leading to an iliac artery-colonic fistula.

In our two patients, in whom laparotomy was not an
acceptable option, embolisation seemed the preferable approach [13]. The reasons for its lack of success did not appear to be any underlying coagulopathy, nor bleeding from collateral blood vessels [14,15]. Emboli of wire coils are more long-lasting than those of Gelfoam. Nevertheless, they failed to cause persistent occlusion of the arterial site of haemorrhage. In retrospect, the use of larger wire coils together with Gelfoam might have been a better approach.

On the horizon is the experimental intra-arterial use of covered stents to bridge the site of arterial disruption by forming an intra-arterial channel (bypass) across the point of bleeding from the lateral wall of an artery. Anatomically, the bleeding site in the splenic artery might well have lent itself to such an approach. The question of durability of such approaches remains to be demonstrated.

Management of patients with radiation-induced gastrointestinal haemorrhage, in patients whose basic disease is currently incurable, obviously poses major problems in judgement. For irradiated patients in whom the cancer has been resected, an aggressive approach would seem advisable.

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References