Fortnightly Review

Management of variceal haemorrhage

Simon G J Williams, David Westaby

Variceal haemorrhage complicates the clinical course of chronic liver disease in about 30% of patients.[1] Mortality for the index bleed is as high as 50%,[2] with a 30% mortality for subsequent recurrent bleeds. The rate of recurrent haemorrhage in those who survive the initial bleeding episode is as high as 100% over two years.

Summary points

- Bleeding varices are a major clinical complication of portal hypertension
- After initial resuscitation the optimal treatment is early therapeutic endoscopy
- If endoscopic expertise is not available drug treatment or balloon tamponade should be used
- Surgical intervention and transjugular intrahepatic portal-systemic stent shunt should be used as "rescue" procedures

Management of active variceal haemorrhage

The initial resuscitation of the patient is of paramount importance, with protection of the airway, particularly in patients with encephalopathy, and restoration of the circulating volume (box 1).

Establishing adequate venous access, in some cases through a central venous catheter, is essential to ensure ease of fluid replacement and adequate monitoring of the patient. In patients with ascites, the elderly patients, and those with associated medical conditions such as ischaemic heart disease, the right atrial pressure may not accurately reflect left sided heart pressures so fluid replacement should be monitored with a Swan-Ganz catheter.

Detailed attention to fluid replacement is important for any gastrointestinal bleed and even more so in patients with established chronic liver disease. These patients may have reduced vascular tone and fail to mobilise pooled venous blood from the splanchnic circulation.[3] Failure to achieve prompt volume replacement may jeopardise renal and hepatic function, a major factor in the morbidity and mortality associated with a variceal bleed.[3] It is equally important to avoid overfilling as this may precipitate rebleeding, so the right atrial pressure should be maintained between 4 and 8 mm Hg.

Immediate transfusion of colloid (crystalloid in the form of saline should be avoided in patients with chronic liver disease because of impaired renal sodium excretion and the development of ascites) should be followed by cross matched whole blood.[3]

After the patient has been resuscitated, early endoscopy, optimally within four hours, enables accurate identification of the bleeding site, which may not always be from varices,[4] and allows informed decisions on treatment (box 2). Such diagnostic endoscopy should be undertaken only by those with the technical skills to perform endoscopic treatment.

Box 1—Initial resuscitation

- Protect airway
- Ensure adequate venous access
- Consider central venous catheter
- Consider Swan-Ganz catheter (in those with ascites or associated medical problem)
- Transfuse (colloid, then cross matched whole blood)

About 60% of patients bleeding from varices will stop spontaneously.[5] Confirmation of a variceal source of bleeding depends on observing an active haemorrhage or finding an adherent fibrin plug or blood clot. A presumptive diagnosis is made if these signs are absent when no other source of blood loss can be identified. If there is evidence of portal hypertension but no obvious site of haemorrhage it is important to document the presence or absence of all potential bleeding points including oesophageal and gastric varices, portal hypertensive gastropathy, and mucosal lesions.

Diagnostic endoscopy offers the earliest opportunity to start treatment both in those who continue to bleed and those who have stopped spontaneously. The results of this approach have been extremely encouraging, with haemostatis achieved in about 90% of patients and reduced rebleeding rates[6] (see below).

Should the expertise to perform early interventional endoscopy not be available then the other options for immediate management include drug treatment and balloon tamponade.[7] These techniques are effective only while they are being applied so arrangements should be made at an early stage for the transfer of the patient, at an appropriate time, to a tertiary centre.

After the initial intervention to arrest haemorrhage careful monitoring for stability of haemodynamic variables and adequate urine output will allow early detection of continued bleeding and hasten further attempts to arrest haemorrhage. The potential for multiple organ failure after variceal haemorrhage also demands care in monitoring the patient for encephalopathy, sepsis, and hepatic and renal failure, with appropriate intervention to treat these complications.

Endoscopic treatment

The choice of treatment depends on the site of the bleeding varices (box 2).

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OESOPHAGEAL VARICES

The management of choice for patients with acute oesophageal variceal bleeding is injection sclerotherapy.[8] Bleeding may be controlled by injecting sclerosant either directly into the varix (intravariceal) or beside the varix (paravariceal), or by a combination. The volume and type of sclerosant used varies, but smaller volumes have been used without loss of efficacy and with fewer complications.

Injection sclerotherapy controls bleeding in up to 95% of cases[8] and reduces rebleeding in hospital, although there is no evidence for an improvement in survival.[9,10]

More recently attention has focused on an alternative approach for the endoscopic management of acute variceal haemorrhage. Endoscopic banding ligation is a modification of the technique used for elastic band ligation of internal haemorrhoids. A cylindrical device is attached to the end of a forward viewing endoscope. A second cylinder with prestressed rubber band is inserted into this and held in place by a trip wire running through the biopsy channel of the endoscope. The bleeding varix is sucked into the the inner cylinder when the device is placed on the varix and suction applied through the endoscope's suction channel, and the band is rolled on to the varix when the trip wire is pulled (fig 1). The entrapped varix will eventually slough off, leaving a small discrete ulcer. An overtube is passed into the proximal oesophagus over the endoscope to allow repeated intubation and banding.

The three completed randomised trials comparing endoscopic banding ligation with injection sclerotherapy show that ligation eradicates varices in fewer treatment sessions, but the techniques do not differ in the acute setting.[11-13] Endoscopic banding ligation is relatively cumbersome and may be time consuming when there is bleeding; passage of the 27 cm overtube may be poorly tolerated, particularly by agitated patients. Furthermore, attachment of the banding device results in a diminished field of vision, which is an important limitation in the presence of blood within the oesophagus. A session of injection sclerotherapy should be the first line endoscopic treatment when there is bleeding. If bleeding has stopped and good views of the varices are obtained endoscopic banding ligation can be used. The benefits of endoscopic banding ligation in the long term are convincing[11-13] and acute injection sclerotherapy should be followed by banding two to three days after the initial procedure. Endoscopic banding ligation, in our experience, is well tolerated soon after injection sclerotherapy.

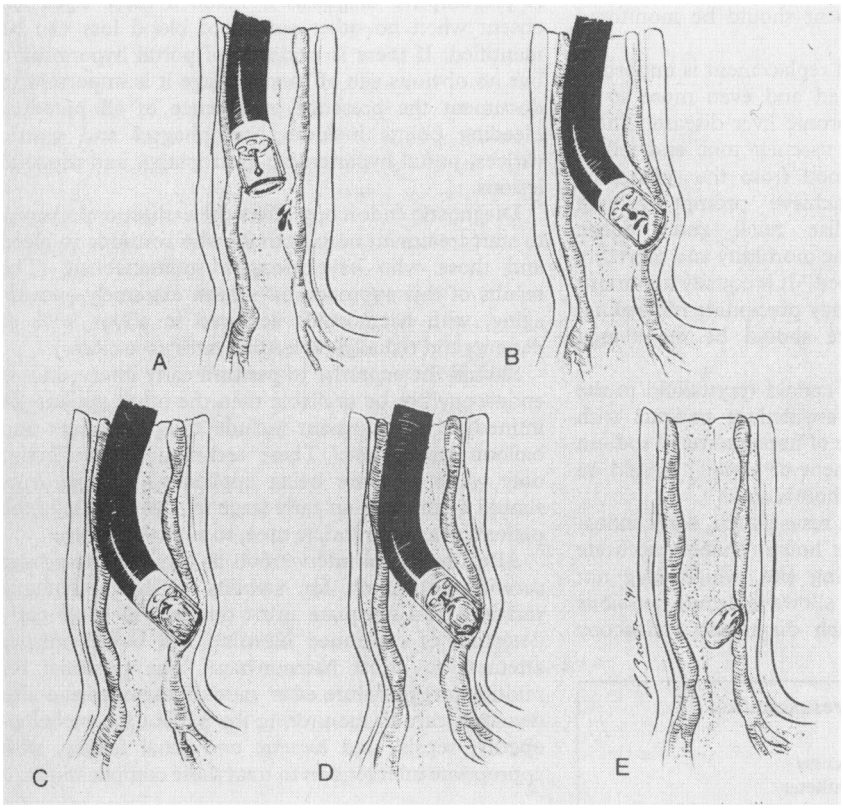

FIG 1—*Endoscopic banding ligation. (A) Identification of bleeding varix; (B) application of ligating attachment to varix; (C) application of suction through endoscope; (D) traction on trip wire, resulting in release of prestressed rubber band and ligation of varix; (E) final result. Endoscope is then withdrawn through overtube, reloaded, and further bands applied to other variceal chords. Reproduced with permission of W B Saunders*

Box 2—Options for initial treatment

If endoscopic expertise is available:
- Oesophageal varices
  - Injection sclerotherapy
  - Banding ligation
- Gastric varices
  - Tissue adhesives
  - Thrombin

If expertise is not available:
- Pharmacological treatment
  - Vasopressin plus nitroglycerin or glypressin
  - Somatostatin or octreotide
- Balloon tamponade

Transfer patient, when stable, to a centre where endoscopic expertise is available

GASTRIC VARICES

The optimum treatment for bleeding gastric varices remains to be defined. Injecting conventional sclerosants has been efficacious for varices situated on the lesser curve of the stomach or within a hiatus hernia, but for fundal or cardia varices this approach has had a high complication rate and poor efficacy.[14]

Two alternative endoscopic strategies have been proposed for bleeding gastric fundal varices. The tissue adhesives N-butyl-2-cyanoacrylate (histoacryl) and isobutyl-2-cyanoacrylate (bucrylate) have been used with some success in uncontrolled series. Control of bleeding has been reported in over 90% of patients.[15] However, there are risks of equipment damage by the tissue adhesives in inexperienced hands. In addition there are report of serious neurological complications attributed to the tissue adhesives.[16] We would resort to their use only in a life threatening situation.

A recent report details the use of direct intravarix injection of bovine thrombin as a means of thrombosing gastric varices. Bovine thrombin, diluted to 1000 U/ml and injected in 1 ml aliquots, successfully controlled bleeding from gastric fundal and lesser curve varices in 11 consecutive patients.[17] This approach does not produce mucosal ulceration, which is a major limitation of sclerosing agents (and also occurs with the tissue adhesives) and is a cause of subsequent rebleeding.[15,18] There is also no evidence for clinically important allergic reactions to repeated injections of thrombin and no evidence of thrombosis distant from the site of injection.[17]

Vasoactive drugs and balloon tamponade

In the absence of expertise for early interventional endoscopy the options for immediate management are drug treatment and balloon tamponade.

DRUG TREATMENT

The potential advantage of vasoactive drugs is that they can be given to patients in whom there is a high suspicion of bleeding varices at the time of presentation. However, none of the currently available agents is effective in all patients, and for many there are

associated side effects. The major limitation of vasoactive drugs is their inability to influence those instances of massive or major haemorrhage.

The most widely used pharmacological agent is vasopressin; when used in conjunction with nitroglycerin it is most conveniently given transdermally (to reduce its systemic side effects while preserving its reduction of portal pressure) and controls variceal haemorrhage in 60-70% of patients.[19] Glypressin, a synthetic analogue of vasopressin, achieves haemostasis in 50-88% of patients; it is more convenient to give as 2 mg boluses every 4-6 hours, and it seems to have a fewer side effects than vasopressin.[19] Glypressin has also been used in combination with nitroglycerin, although this is not common clinical practice.

More recently somatostatin and its synthetic analogue octreotide have been advocated for the control of bleeding. A continuous infusion of somatostatin controls bleeding in 40-77% of cases,[19] and similar results have been obtained for octreotide.[20,21] These agents have the major advantage that they have very few side effects.[19]

Recent studies suggest similar efficacy for drugs as for injection sclerotherapy, but interpretation of the results is difficult because a high proportion of the patients had spontaneously stopped bleeding before randomisation and the trials emphasised the prevention of early rebleeding. Current evidence suggests that the available drugs are safe and easy to use, with proved efficacy, but immediate injection sclerotherapy remains the treatment of choice for variceal bleeding. Drugs should be used when endoscopic expertise is not available or as an adjunct to further treatment if continued variceal haemorrhage is suspected. It is also possible that drugs have a role in reducing early rebleeding after injection sclerotherapy.[22]

BALLOON TAMPONADE

Balloon tamponade achieves control of variceal bleeding by direct pressure on the varices and can be life saving in the patient who presents with massive haemorrhage. In experienced hands it is highly effective, with control of bleeding in 90% of cases.[23] However, up to 50% of patients rebleed when the tube is deflated, and there is an associated complication rate of 25-30%.[24] Serious complications such as oesophageal perforation or ulceration and aspiration pneumonia may occur in up to 15% of patients.

The gastric balloon is the most important factor for controlling bleeding. The balloon is inflated with 120-200 ml water (containing a small amount of radiographic contrast to enable it to be seen more easily on radiographs) and needs to be placed close to the oesophagogastric junction to arrest cephalad blood flow. We use a tube with both gastric and oesophageal balloons (Sengstaken-Blakemore) but inflate the oesophageal balloons only if bleeding is not controlled. If gastric varices are the source of haemorrhage a tube with a single large (600 ml) gastric balloon (Linton-Nachlas) is more effective in stopping haemorrhage.[25]

The balloon should not be inflated for more than 18 hours. Alternative, definitive treatment must be planned for when the balloon is deflated.

Transjugular intrahepatic portal-systemic stent shunt

Recent reports of the use of transjugular intrahepatic portal-systemic stent shunt in the control of acute variceal haemorrhage have challenged the place of acute variceal sclerotherapy in the treatment of bleeding varices.

With the patient sedated the right internal jugular vein is cannulated. A catheter is advanced into a hepatic vein and a needle is then advanced into a portal vein branch by using fluoroscopy as guidance. Once a portal-systemic tract has been established, it is dilated up to 10 mm by using an angioplasty balloon, and one or two metal stents are inserted to maintain patency.

The need for experienced operators, who can successfully complete this technically demanding procedure in over 90% of patients, means that the technique is unlikely to become widely available. Active variceal bleeding can be controlled in up to 90% of patients but will recur in 10-20%. Overall mortality is 25-30%, although mortality directly related to the procedure is much lower.[26]

The major limitations reflect the problems associated with the construction of a total portal-systemic shunt. Encephalopathy has been documented in up to 20% of patients over short periods of follow up.[26] The larger calibre (10 mm) shunts are associated with higher encephalopathy rates, and attempts at reducing this with smaller calibre (8 mm) shunts may result in higher rebleeding rates.

Shunt stenosis may occur in up to 15% of patients and may progress to occlusion in 10%, with associated risks of rebleeding.[26] Shunt stenosis may be managed by further balloon dilatation of the stent or with further stent placement.

Appropriate comparison of this procedure with sclerotherapy is likely to be difficult and the two techniques should probably be regarded as complementary. Currently, in our opinion, transjugular intrahepatic portal-systemic stent shunt should be used as a "rescue" procedure in patients who continue to bleed despite two sessions of endoscopic intervention (box 3).

Surgical intervention

Few would not advocate surgical intervention as first line treatment for variceal haemorrhage. Although there is no mortality benefit for patients treated endoscopically when compared with those treated surgically, the widespread availability and ease of therapeutic endoscopy have favoured endoscopic techniques.

Surgery is now confined to those patients who continue to bleed despite endoscopic intervention (box 3). Mortality for continued bleeding in this cohort, after two episodes of endoscopic treatment (over a short period of time), approaches 90% in patients of Child's grade C.

Current surgical techniques include oesophageal transection with or without devascularisation, which in comparison with injection sclerotherapy has been shown to reduce early rebleeding significantly but to produce no survival advantage.[27] The portal-caval shunt carries a high mortality in the emergency situation (33-56%), although more recent uncontrolled data shows reduced perioperative mortality (9%) in patients undergoing early shunt procedures.[27] This improvement may reflect improved perioperative and postoperative care.

Some centres still advocate the use of shunt surgery as first line treatment for bleeding varices, and though controlled comparison of shunt surgery with injection sclerotherapy shows reduced rebleeding in the surgically treated group there is no long term beneficial effect

Box 3—Options for continued bleeding

- Transjugular intrahepatic portal-systemic stent shunt
- Oesophageal transection with or without devascularisation
- Portal-caval or selective shunt

Choice of option depends on local expertise

on survival. In addition, the surgically treated group had an increased frequency of liver decompensation due to the consequent reduction in hepatic perfusion.[27]

The selective distal spleno-renal shunt was developed to reduce rates of encephalopathy. While there is no consensus on whether or not encephalopathy rates are reduced by creating a selective shunt, the major limitation of this procedure is that it is technically demanding to perform and carries a high perioperative mortality in the emergency situation.[27]

Selection of a surgical intervention should involve consideration of whether orthotopic liver transplantation is a prospect. In suitable cases the aim should be to select procedures, such as the mesocaval or selective distal spleno-renal shunt, that do not affect the liver hilum.

Transplantation

Transplantation can successfully treat bleeding varices and represents a "cure" of the problem.[28] Patients already selected for transplantation on the basis of reduced hepatic reserve are particularly appropriate for this form of treatment and have survival rates better than those achieved with other forms of surgical intervention.[28] However, in a few patients other techniques cannot control variceal bleeding and prevention of recurrent variceal bleeding is simply a consequence of orthotopic liver transplantation rather than a specific indication for it.

Ectopic varices

Varices found at sites other than the oesophagus and stomach account for 3% of patients with haemorrhage (box 4).[29] Varices may be found within the small bowel, colon, and rectum; at sites of previous surgery such as stomas and within adhesions (peritoneal varices), and in association with the bile duct (choledochal varices).

Box 4—Ectopic varices

- Account for 3% variceal bleeding episodes
- Are often inaccessible to endoscopic treatment
- May require surgical intervention
- May stop bleeding with pharmacological treatment

Failure to recognise ectopic varices as a potential source of bleeding frequently leads to a delay in treatment. Treatment is governed by the ability to attain direct endoscopic access, and in many cases surgical intervention is needed. Pharmacological agents have been used.[29] Bleeding from ectopic varices may be an indication for the use of drugs in patients with known portal hypertension before the site of bleeding has been confirmed.

Summary

Fig 2 gives an algorithm for the treatment of bleeding oesophageal varices. Initial resuscitation of the patient is of paramount importance, ideally followed by early interventional endoscopy. Recent advances in available endoscopic techniques enable the endoscopist to suit the therapeutic approach to the clinical situation.

Injection sclerotherapy remains the initial treatment of choice in bleeding patients. Endoscopic banding ligation is an alternative, best used in patients who have spontaneously stopped bleeding or as a complementary treatment a few days after the initial session of injection sclerotherapy. The tissue adhesives and thrombin can be used to treat bleeding gastric varices.

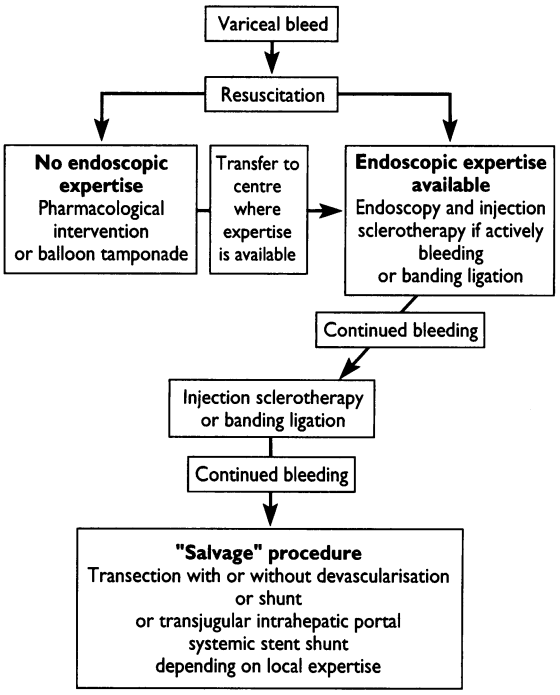

FIG 2—*Algorithm for management of actively bleeding oesophageal varices*

Should the endoscopic expertise not be available, drug treatment (with somatostatin or octreotide) or balloon tamponade are the treatments of choice.

Transjugular intrahepatic portal-systemic stent shunt is a new effective technique, not yet widely available, which has a documented complication rate that has yet to be fully defined. It is a good alternative to surgery as a "rescue" procedure for patients who continue to bleed depite two sessions of endoscopic intervention.

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Current Issues in Cancer

Genes, dreams, and cancer

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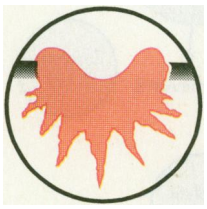

This is the eighth in a series of articles examining developments in cancer and updating what we know about the disease

There have been tremendous advances in our understanding of cancer from the application of molecular biology over the past decade. The disease is caused by a series of defects in the genes that accelerate growth—oncogenes—and those that slow down cellular turnover—tumour suppressor genes. The proteins they encode provide a promising hunting ground in which to design and test new anticancer drugs. Several treatment strategies are now under clinical trial entailing direct gene transfer. These include the use of gene marking to detect minimal residual disease, the production of novel cancer vaccines by the insertion of genes which uncloak cancer cells so making them visible to the host's immune system, the isolation and coupling of cancer specific molecular switches upstream of drug activating genes, and the correction of aberrant oncogenes or tumour suppressor genes. The issues in these approaches are likely to have a profound impact on the management of cancer patients as we enter the next century.

The key problem in the effective treatment of patients with solid tumours is the similarity between tumour cells and normal cells. Local procedures such as surgery and radiotherapy may be effective, but only if the malignant cells are confined to the area treated. This is so in around one third of cancer patients. For most, some form of systemic selective therapy is required. Though many cytotoxic drugs are available, only a small proportion of patients are actually cured by them. The success stories in Hodgkin's disease, non-Hodgkin's lymphoma, childhood leukaemia, choriocarcinoma, and germ cell tumours have simply not materialised for the common cancers such as those of the lung, breast, or colon. And this is despite enormous efforts in new drug development, clinical trials of novel drug combinations, the addition of cytokines, high dose regimens, and even bone marrow rescue procedures.

Molecular biology of cancer

Against this disappointing clinical backdrop there has been a dramatic increase in information on the molecular biology of cancer. Oncogenes were first discovered in the RNA tumour viruses of chickens, cats, and rodents. Oncogenes encode a series of molecular cogs that control the growth of cells by transmitting signals from the cell surface through to the nucleus. Mutations which lead to oncogene products with increased activity or their excess production may result in abnormal growth patterns and cancer.[1] The more recently discovered tumour suppressor genes encode proteins that act as the cell's braking system.[2] When these are deleted, down-regulated, or mutated abnormal growth may again be the outcome (fig 1). Probably four to six genetic changes are necessary to produce most human cancers. Though our knowledge of growth control is still rudimentary, we have at last had the first glimpse of its complexity. This has brought a new vision with which to develop novel selective mechanisms to destroy tumours.

There are many potential avenues to follow in devising future treatments. The first is to learn how the growth signalling apparatus works in detail and to develop drugs that can target specific components within it. Examples being actively pursued include the construction of growth factor analogues which can slow growth by competitively binding to receptors[3] and dimerisation inhibitors to block cell surface receptor

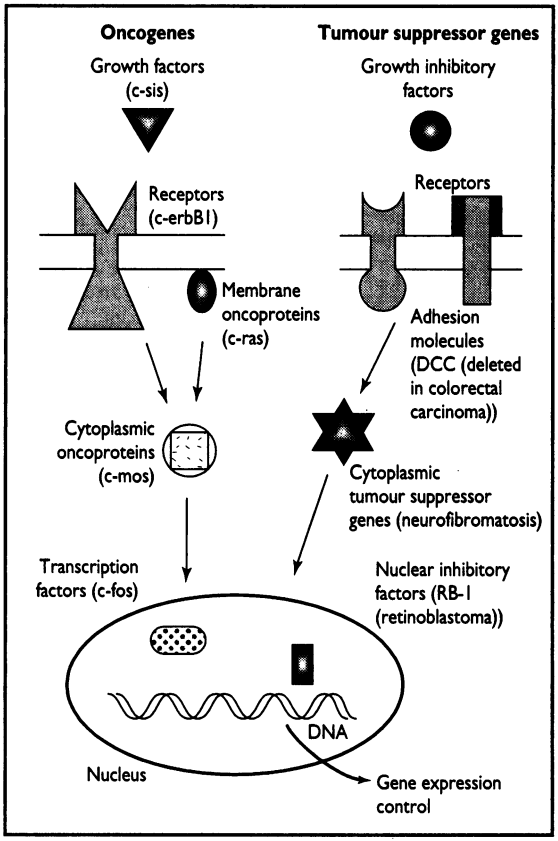

FIG 1—*Interacting pathways of oncogenes and tumour suppressor genes*

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