Classic diseases revisited

Chronic pancreatitis: diagnosis and treatment

Summary

Three-dimensional magnetic resonance cholangiopancreatography is currently the most exciting new imaging technique for chronic pancreatitis. Endoscopy-assisted duodenal intubation during the secretin-cholecystokinin test reduces intubation time in difficult cases. The NBT-para-amino benzoic acid test has been refined to enhance its discriminant power. The cholesteryl-[C¹³]octanoate breath test and the faecal elastase test are newer highly sensitive and specific tubeless tests.

Pain in chronic pancreatitis continues to be a vexing therapeutic issue. Enzyme treatment continues despite criticism. Neurotensin is the new suspected mediator of the feedback mechanism, which is down-regulated by enzyme therapy. Steroid ganglion block is an exciting therapeutic tool for pain relief. Endoscopic pancreatic sphincterotomy, Dormia basketing and pancreatic stenting in conjunction with extracorporeal shock wave lithotripsy should be performed early in chronic pancreatitis to prevent parenchymal atrophy with ensuing exocrine and endocrine pancreatic dysfunction. The modified Puestow's procedure preserves endocrine and exocrine pancreatic functions besides relieving pain. Closed loop insulin infusion allows superior management of pancreatic diabetes following near total pancreatectomy. The standardised incidence rate of pancreatic cancer is 16.5 in patients with alcoholic chronic pancreatitis and 100 for tropical chronic pancreatitis. Aggressive treatment protocols combining neo-adjuvant chemoradiation and intra-operative radiation with surgery are being used to improve the prognosis in this dismal complication of chronic pancreatitis.

Keywords: pancreatitis, pancreatic cancer, pancreatic function, pain

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Chronic pancreatitis is prevalent in most parts of the world although its aetiology and clinical course may vary in different regions. Community-based field studies from our centre have revealed that tropical chronic pancreatitis in Southern India is a mild disease with onset of symptoms in early adulthood,¹ and a prevalence of 1:793 in endemic areas. The predominant symptoms are abdominal pain (30.6%), diabetes mellitus (52.8%) and malabsorption (16.7%).¹ On the other hand, patients presenting to office practice,² or to local or tertiary care hospitals³ have severe chronic pancreatitis, with abdominal pain as the predominant symptom (approximately 80%); exocrine pancreatic insufficiency and calcification are seen in 80–90% patients.² In a recent study,³ surgical treatment for pain was required in 53.9% of chronic pancreatitis patients referred to the All India Institute of Medical Sciences, a leading tertiary care centre in Northern India.

Chronic pancreatitis is incurable except in some specific situations such as hyperparathyroidism where cure can be expected with surgical removal of the parathyroid glands. Alcohol withdrawal may slow down, but not reverse the progressive damage to the pancreas. Nevertheless, rapidly advancing knowledge of the pathogenesis of chronic pancreatitis now allows us to adopt a multidimensional strategy for its management. Therapeutic strategies in chronic pancreatitis (box 1) are discussed below with emphasis on recent developments in diagnosis and treatment.

Diagnosis

CONVENTIONAL PANCREATIC IMAGING

Plain film of the abdomen for pancreatic calcification, sonography, computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) remain the mainstay of diagnosis of chronic pancreatitis. Recently, on comparing 1.5-T magnetic resonance imaging (MRI) with dynamic gadolinium enhancement, with CT and ERCP, Semelka *et al*⁴ found MRI scanning to be most sensitive and specific in detecting pancreatic diseases.

MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY (MRCP)

MRI is utilised in this latest and most exciting technique to visualise the pancreatic and biliary ductal systems. It is bound to have a significant impact on the diagnosis and management of biliary and pancreatic diseases.⁵ Important features of the technique are summarised in box 2.

MRCP offers a precise, noninvasive, three-dimensional coronal and frontal display of pancreatic and biliary ductal systems.

SERUM LEVELS OF PANCREATIC ENZYMES

Depressed serum levels of pancreatic isoamylase, lipase, and pancreatic polypeptide aid in the diagnosis of chronic pancreatitis. Elastase, deoxyribonuclease and ribonuclease are elevated, along with an increased trypsin/creatinine clearance ratio.⁶

LACTOFERRIN ASSAY

Elevated levels of lactoferrin in the pure pancreatic juice and an increased lactoferrin to lipase ratio in duodenal juice following secretin–cerulein stimulation⁷ have been claimed to be very sensitive and specific for detecting early chronic pancreatitis.

PANCREATIC ENZYME SYNTHESIS

Demonstration of an increased rate of pancreatic enzyme synthesis using radiolabelled amino acids is another highly sensitive index of early chronic pancreatitis.⁸

Chronic pancreatitis:
therapeutic strategies

- symptomatic relief of pain
- management of exocrine and endocrine insufficiency
- therapeutic interception of pathophysiology
- management of complications

Box 1

Fast MRCP

- individual image pixels assigned a high signal to represent ducts
- signal intensities adjusted to give a volumetric appearance
- post acquisition data processing using a maximum intensity projection algorithm
- a three-dimensional work station allows the image to be rotated and pruned of peripheral branches so that strictures and stones can be clearly delineated in both common bile duct and main pancreatic duct

Box 2

Pancreatic tubeless tests:
refinements & innovations

NBT-PABA test

- administration of 30 mg/kg rather than 15 mg/kg improves its discriminant power
- spectrofluorometric estimation of para-aminosalicylic acid & PABA in plasma shortens the test time

Cholesteryl-C¹³-octanoate breath test

- based on intraluminal hydrolysis of cholesterol-C¹³-octanoate by pancreatic cholesterol esterase
- estimation of ¹³CO₂ in breath

Combined cholesterol-C¹³-octanoate + NBT-PABA tests

- exocrine pancreas function may be over or underestimated if these tests are applied singly
- pancreatic enzymes do not decrease simultaneously in chronic pancreatitis

Faecal elastase (E1) test

- determined by a new electroimmunoassay
- spot stool E1 activity of controls 15 to 500 µg/g stool

Box 3

PANCREATIC FUNCTION TESTS (BOX 3)

The secretin–cholecystokinin stimulation test with duodenal intubation remains the gold standard for diagnosing chronic pancreatitis. Recently, Madrazo-de la Garza *et al*⁹ reduced the length of the study from 150 to 45 minutes by aspirating duodenal fluid through a fibre-optic endoscope. Since endoscopy is costly and adds to the discomfort, Dimagno *et al*¹⁰ have suggested the use of endoscopy only during intubation difficulties. In the latter situation they would endoscope patients, place a guidewire in the duodenum, withdraw the endoscope, slide the aspiration tube over the wire and then perform the test as usual. This reduces the intubation time and also the frequency of performing endoscopy to test the pancreatic functions.

The Lundh test meal continues to be performed in several centres as a cheap and effective alternative to the secretin test while recognising its relative insensitivity in early chronic pancreatitis.¹¹ Tubeless tests such as the NBT-para-aminobenzoic acid (PABA) test and pancreolauryl test^{12–14} are easy to perform and convenient to the patients, although the kits are not easily available and are expensive. Moreover the NBT-PABA test remains a test of protein malabsorption of end-stage chronic pancreatitis.

Faecal chymotrypsin assay is a cheap test of pancreatic exocrine dysfunction with a sensitivity of 49% in early and 80–90% in advanced chronic pancreatitis.

The cholesteryl-C¹³-octanoate breath test is a recent innovative addition to the category of highly sensitive and specific noninvasive tests of pancreatic exocrine function.^{15,16}

Most recently, the potential and precision of faecal elastase test in comparison with the secretin–pancreozymin test in the diagnosis of chronic pancreatitis was evaluated.¹⁷ There was good correlation between the output of faecal elastase and that of amylase, lipase and trypsin. Patients with chronic pancreatitis had significantly lower concentrations of enzyme than normal controls. No significant decrease of immunoreactivity was found when stool samples were stored at room temperature for over a week. In contrast to faecal chymotrypsin, the test results are unaffected by pancreatic enzyme replacement therapy.

Palliation of pain in chronic pancreatitis

A better understanding of the pathophysiology and pathogenesis of chronic pancreatitis has revitalised therapeutic plans to palliate pain. Hence it is necessary to recapitulate the currently understood pathogenic mechanisms of pain before discussing its management.

MECHANISMS OF PAIN (BOX 4)

Ductal hypertension

In the normal human pancreas, unstimulated main duct pressure is about 7 mmHg. Bradley found that the mean ductal pressure was 25 mmHg in 19 patients with painful chronic pancreatitis and a dilated pancreatic duct.¹⁸ Ductal strictures and/or calculi cause obstruction and ductal hypertension. However, ductal hypertension can occur in structurally normal pancreatic ducts and painful chronic pancreatitis. The restrictive effect of the parenchymal fibrosis in chronic pancreatitis is like a ‘compartment syndrome’.

Ischaemic theory of pain

Using a hydrogen gas clearance technique, the basal pancreatic blood flow was 40% lower in chronic pancreatitis than in the normal pancreas.¹⁹ Secretory stimulation caused an additional 14% decrease in pancreatic blood flow.¹⁹ The parenchymal ischaemia could be the basis for the continued damage seen even after patients stop drinking alcohol. The dramatic pain relief associated with duct decompression through surgery could be related to an improvement in pancreatic blood flow.

Perineural inflammation hypothesis

This recent attractive hypothesis is based on the disproportionate eosinophilic infiltration of pancreatic nerve plexuses.²⁰ The eosinophils release cytotoxic enzymes which result in neuronal oedema and loss of perineurium.²⁰ This permits the nerves to be irritated by a variety of noxious agents present in the tissues, such as histamine, pancreatic enzymes, and prostaglandins, causing pain.

Pseudocysts

Pseudocysts can cause pain due to elevated intracystic pressures or pancreatic ductal obstruction.

Mechanisms of pain in chronic pancreatitis

- ductal hypertension
- parenchymal ischaemia
- eosinophilic perineural inflammation
- pseudocysts - elevated intracystic pressure

Box 4

CONSERVATIVE MANAGEMENT OPTIONS

Prior to initiating treatment for pain in chronic pancreatitis, a full appraisal is necessary, including severity, frequency, duration of pain and resultant loss of work, ie, performance status. A scoring system has been used at our centre for this purpose.³ Such comprehensive information allows us to select appropriate treatment modalities, conservative or surgical.

Abstinence from alcohol

Abstinence halts the progress of alcoholic chronic pancreatitis leading to pain relief in a fair number of patients.

Diet

A diet of four or five high carbohydrate, low fat and low protein meals per day may assist pain relief.

Analgesics

Nonnarcotic analgesics provide partial relief while other therapies are being enforced.

Pancreatic enzyme therapy

It is not clear whether pancreatic enzymes given to humans reduce pancreatic secretion through a feedback mechanism that down-regulates cholecystokinin release.²¹ Proponents of enzyme therapy argue that patients with ‘small duct disease’ (early chronic pancreatitis) have pain due to elevated cholecystokinin levels. Ingested proteolytic enzymes hydrolyse cholecystokinin-releasing factor and a monitor peptide secreted by the pancreas which together normally stimulate release of cholecystokinin. This results in reduced levels of cholecystokinin and relief of pain. In contrast, patients with ‘large duct disease’ (advanced chronic pancreatitis) do not respond to enzyme therapy. The paradox is that if a feedback mechanism is operative which is enzyme dependent, cholecystokinin levels should be increased in patients with advanced chronic pancreatitis, although they are actually reduced.²² In contrast, neurotensin, a hormone that also stimulates pancreatic secretion, increases postprandially and is decreased by ingesting pancreatic enzymes. These data suggest that neurotensin rather than cholecystokinin might be the mediator of the putative feedback mechanism in humans. Although the available data are certainly not convincing, pancreatic enzymes are used by even the severest critics of this treatment because they are harmless,²¹ improve the patient’s nutritional status, and ameliorate the steatorrhoea.²³ However, this therapy is expensive and harder data are needed to support their continued use. Pitchumoni recommends a month of enzyme therapy alone. If not effective, sodium bicarbonate or H2 receptor antagonists should be added as supplements before recommending surgery.²¹

Experimental modalities

Coeliac ganglion block Destruction of the coeliac plexus by alcohol and phenol injections under radiographic guidance produced controversial results and complications. Hence it is no longer recommended for the palliation of pain in chronic pancreatitis. An injected steroid coeliac ganglion block effectively palliates pain if performed before narcotic dependence sets in.²⁴ Moreover, unlike an alcohol block, it does not complicate resectional surgery.

Octreotide This long-acting somatostatin analogue reduces pancreatic secretion by 50%. Somatostatin directly inhibits secretion of pancreatic acinar cells by preventing secretin-induced cyclic AMP production.²⁵ Therefore octreotide may complement pancreatic enzyme therapy by further suppressing pancreatic secretion.

Cholecystokinin receptor antagonists Proglumide analogues have been used in some cases²⁶ based on the premise that down-regulation of cholecystokinin can reduce pancreatic secretion and palliate pain. However, no randomised controlled studies have been carried out using these agents and their role in palliation of pain remains to be proven.

Oral pancreatic stone dissolution Attempts at oral dissolution therapy for pancreatic calculi to relieve pain have met with very limited success. Sahel and Sarles²⁷ used oral citrate with no therapeutic benefit. Noda²⁸ attempted dissolution with trimethadione (1 to 1.5 g/day for nine months) with mixed results.

Palliation of pain in chronic pancreatitis: promising innovations

- steroid coeliac ganglion block
- octreotide administration
- endoscopic interventions
- extracorporeal shock wave lithotripsy

Box 5

Endoscopic treatment Complete stone clearance from the main pancreatic duct using endoscopic sphincterotomy and Dormia basketing has been achieved in up to 82% of cases.²⁹ In patients with chronic pancreatitis and stricturing of the main pancreatic duct, pancreatic stenting results in clinical improvement in 70–80% of cases. Complete resolution of strictures is not necessary for symptomatic improvement. Stent dysfunction, however, remains a frequent late complication (55%).³⁰ Endoscopic cystogastrostomy or cystoduodenostomy achieves a technical success rate of 98% with resolution of the pseudocysts responsible for pain in 84%. More recently, transpapillary drainage has been described for communicating pseudocysts.³¹

Several recent papers have critically analysed the indications and results of endoscopic therapy of pancreatic diseases.³² The general consensus today is that these are still experimental and should be performed only in a setting of prospective randomised trials.

Extra-corporeal shock wave lithotripsy (ESWL) This is a successful noninvasive new treatment option for pulverising main pancreatic duct calculi.³³ However, it should be performed early to prevent parenchymal atrophy and consequent exocrine and endocrine dysfunction.³⁴ ESWL is usually combined with endoscopic sphincterotomy and Dormia basketing of stone fragments.

SURGERY FOR PAIN

Drainage surgery is the conventional definitive approach to persistent severe pain in chronic pancreatitis. Widdison *et al*³⁵ suggest that drainage procedures relieve pain not only by reducing ductal hypertension, but also by increasing pancreatic blood flow. Machi *et al*³⁶ have exploited the recent innovation of intra-operative ultrasound in identifying the location of the main pancreatic duct.

At our centre, out of 126 consecutive patients with chronic pancreatitis during 1984–1994 (81 tropical and 40 alcoholic), 69 (54.8%) patients underwent surgery for refractory pain.³ Modified Puestow's operation was performed on 56 patients, modified Puestow's with distal pancreatectomy in four, Duval's procedure on seven and distal pancreatectomy alone in two. Postoperative follow-up data over a five-year period were available from 50 patients. Postoperatively, 45 (90%) patients reported adequate pain relief at three months, while 41 (82%) patients experienced significant long-lasting pain relief. Pain recurred in 8% of patients due to anastomotic stenosis (two patients), retained pancreatic duct calculi and pancreatic abscess (one patient) and pancreatic carcinoma (one patient).

Recent literature reports similar efficacy. Cattaneo *et al*³⁷ recorded good resolution of pain in 84.6% of chronic pancreatitis patients with a predominantly (73.7%) alcoholic aetiology (average postoperative follow-up 75.8 months).

Pancreatitis-associated neuritis is a recent concept proposed to account for pain in chronic pancreatitis. Eosinophilic infiltration of pancreatic neuronal plexuses with release of neurocytotoxins such as major basic protein, eosinophilic cationic protein and other proteases, destroys the perineurium and causes axonal oedema.²⁰ The bare axons are exposed to histamine and pancreatic enzymes causing neural irritability and pain. This concept explains the success of pancreatic resection in relieving intractable pain after having failed a drainage procedure. Pylorus and duodenum preserving proximal resection of the pancreas for chronic pancreatitis is a recent innovation. It results in decreased morbidity and mortality coupled with improved ductal drainage of the relatively normal part of the pancreas.³⁸

Management of pancreatic insufficiency

EXOCRINE INSUFFICIENCY

Steatorrhoea can be abolished by administering orally at least 10% of the total amount of lipolytic activity normally secreted postprandially along with an H₂-receptor antagonist to inhibit gastric acid secretion. Omeprazole plus pancreatic enzyme therapy may be ideal in pancreatic exocrine insufficiency associated with hyperchlorhydria, such as in cystic fibrosis³⁹ and idiopathic chronic pancreatitis. Various studies emphasize that there is no ideal pancreatic enzyme preparation. Microencapsulated preparations do not appear to have any added advantage. Delchier *et al*⁴⁰ observed that the enteric-coated preparations did not alter fat absorption in the duodenum as compared with placebo. The standard practice is to first use an uncoated preparation; if steatorrhoea continues following the addition of an H₂ blocker/omeprazole, then microencapsulated preparations should be used. The cholesteryl-C¹³-octanoate breath test¹⁵ can be used to monitor enzyme replacement therapy in patients with steatorrhoea.

ENDOCRINE INSUFFICIENCY AND PANCREAS TRANSPLANTATION
In patients undergoing a total or near total pancreatectomy for chronic pancreatitis, intraportal islet autografts may prevent diabetes.⁴¹ A major problem is the availability of islets in the diseased gland. Rejection criteria following pancreatic transplants include increasing blood glucose, decreasing serum amylase and histopathological evidence of endothelitis and endarteritis obliterans.⁴² An insulin/glucagon ratio of less than 1.0 appears to be specific for recurrent disease.⁴² In the final analysis, closed insulin loop infusion is possibly a better option for post-pancreatectomy diabetes.

Therapeutic interception of pathophysiology

Currently the stress is on identifying ways and means of intercepting the pathophysiological process in chronic pancreatitis. Cessation or reversal of the disease process is the final goal.

Therapeutic interception of chronic pancreatitis pathophysiology

- drainage surgery to preserve exocrine and endocrine pancreatic functions
- endoscopic intervention in chronic obstructive pancreatitis
- treatment associated with metabolic aetiologies (hyperlipidaemia, hyperparathyroidism)
- micronutrient – antioxidant ‘cocktail’
- anticholinergic therapy

Box 6

DRAINAGE OPERATION FOR LARGE DUCT CHRONIC PANCREATITIS
A recently updated retrospective study⁴³ of a large group of patients - either observed or decompressed, suggests that Puestow’s procedure delays progressive loss of exocrine and endocrine fuction in chronic pancreatitis. The same group also described a prospective, randomised trial of drainage surgery versus observation for patients with large-duct, mild to moderate, chronic pancreatitis who had disabling pain. Progressive impairment of exocrine and endocrine function or worsening of ductal morphology was recorded in only two out of nine patients undergoing a modified Puestow’s procedure (table 1). On the other hand, six out of the eight nonsurgically treated patients worsened in terms of the parameters of chronic pancreatitis over a mean follow-up of 39 months. Similar results have emerged from a much larger prospective study of response to drainage surgery in chronic pancreatitis which was concluded recently at our centre.³ Besides relief of pain in 41/50 patients, improvement in diabetes mellitus was noted in five/11 patients over a longer follow-up period of five years (table 2). Even in the remaining six patients with diabetes mellitus, blood glucose levels and insulin requirements stabilised. The final conclusion emerges that pain relief may no longer be the only reason for performing a drainage procedure.⁴⁴ We concur that the role/indications of Puestow’s procedure can be redefined to preserve endocrine and exocrine pancreatic functions, in addition to relieving pain.³

ENDOSCOPIC MANAGEMENT
Endoscopic sphincterotomy, balloon dilation and stenting offer definitive therapy for chronic obstructive pancreatitis secondary to papillary stenosis and focal pancreatic ductal strictures caused by trauma or acute pancreatitis. However, sepsis may develop and stents occasionally migrate into the main pancreatic duct, thereby occluding the side branches of the main pancreatic duct leading to exacerbations of chronic pancreatitis.³⁰

Table 1 Prospective evaluation following modified Puestow’s procedure in patients with mild to moderate chronic pancreatitis with minimal pain*

Study group (n)	Baseline evaluation** n (%)	Follow-up evaluation** n (%)
Operated (9)	9 (100)	7 (78)
Nonoperated (8) (observation only)	8 (100)	2 (25)

*Modified from Nealon and Thompson.⁴³ **Number (%) of chronic pancreatitis patients with mild to moderate severity at initial and follow-up evaluation; mean follow-up 39 months.

Table 2 Prospective evaluation following modified Puestow’s procedure in patients with severe chronic pancreatitis, predominantly (64.3%) tropical*

Parameters	Postoperative evaluation**
Relief of pain, n/N (%)	41/50 (82)
Improvement in diabetes mellitus, n/N (%)	5/11 (45.4)
Improvement in steatorrhoea, n/N (%)	1/6 (16.9)

*Modified from³. **Mean follow up period 5 years. N=number of patients studied, n=number of patients who had improvement

MANAGEMENT SECONDARY TO METABOLIC ABERRATIONS

Appropriate therapy of hyperlipidaemia and parathyroid resection for hyperparathyroidism can halt or reverse chronic pancreatitis secondary to such metabolic defects.

ANTIOXIDANT THERAPY

This is a novel concept based on the oxidant stress theory in the pathogenesis of chronic pancreatitis. Uden *et al*⁴⁵ succeeded in decreasing pain in recurrent pancreatitis by administering a micronutrient antioxidant cocktail therapy composed of 600 µg organic selenium, 9000 IU beta-carotene, 0.54 g vitamin C, 270 IU vitamin E, and 2 g methionine to their patients.

ANTICHOLINERGIC TREATMENT

The recent demonstration of the role of the cholinergic mechanism in inducing pancreatic secretion⁴⁶ offers hope that anticholinergic drugs may modify the disease process of chronic pancreatitis and relieve pain.

Management of complications of chronic pancreatitis

Pancreatic pseudocysts constitute the most common complication of chronic pancreatitis, occurring with an incidence of 20–40%. The role of surgery in the modern management of pseudocysts was reviewed recently by Grace and Williamson.⁴⁷ They concluded that asymptomatic chronic pseudocysts 6 cm or less in diameter do not require intervention whereas those that are symptomatic, enlarging, or more than 6 cm in diameter should be treated. They recommend treating such pseudocysts with internal drainage using a Roux-en-y cystojejunostomy.

Recently, a number of nonoperative alternatives have been promoted such as one time percutaneous aspiration and percutaneous catheter drainage alone or in combination with parenteral octreotide.⁴⁸ Percutaneous catheter drainage is, however, often associated with repeated episodes of drain tract infection.⁴⁴ Endoscopic cystoduodenostomy may be the treatment of choice in patients where the pseudocyst impinges on the duodenum and is closely adherent to it, particularly if these patients are poor surgical risks.

Benign lower end strictures of the common bile duct due to chronic pancreatitis can be endoscopically dilated/stented or surgically rectified by employing a Roux-en-y choledochojejunostomy. Vascular complications such as splenic vein thrombosis with symptomatic sinistral portal hypertension can be easily resolved with splenectomy alone. Haemosuccus pancreaticus, either intermittent and massive or chronic, can be controlled with embolisation or surgical ligation and resection.

Infrequent complications such as gastric outlet obstruction and transverse colonic stricture can be suitably rectified by employing a surgical by-pass procedure.

Pancreatic carcinoma arising as a complication of chronic pancreatitis is the subject of several recent important studies. A recent multicentre historical cohort study involving 2000 patients with chronic pancreatitis from five European countries and the US found that the risk of developing pancreatic cancer is significantly elevated.⁴⁹ Another recent study from Madras, India, found the risk of pancreatic cancer in patients with tropical chronic pancreatitis to be 100 times greater than expected.⁵⁰ This confirmed earlier reports on the malignant potential of tropical chronic pancreatitis which is prevalent in India, and other Asian and African countries. Thus, for patients with alcoholic and idiopathic chronic pancreatitis, the standardised incidence rate was 16.5; for those with tropical chronic pancreatitis it was 100.

Surgery continues to offer the only possibility of cure. However, most patients still have local recurrence after resection. Currently more aggressive treatment protocols combining neo-adjuvant chemoradiation and intra-operative radiation with surgery are being used.⁵¹

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