ASSOCIATION OF PHYSICIANS OF INDIA
KERALA CHAPTER

FROM EDITOR'S DESK

Dear friends,

2019 has passed in the blink of an eye.

Natural disasters were not so bad as 2018. The present demand is for abolishing plastics from our day to day life; at least the single use ones.

We owe it to our next generation to preserve nature as best as we can. In the most livable form possible.

Conserve the forests, reduce cutting down of trees, use natural resources of energy as far possible.

Judicious use of antibiotics is another plea. We have had too many drug resistant bugs in this decade. Not many new antibiotics are in the offing. Antibiotic stewardship and conservation should be our motto.

Wishing each and everyone of you a very happy and prosperous new year.

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LATE COMPLICATIONS OF BARIATRIC SURGICAL OPERATIONS

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INTRODUCTION

The number of bariatric surgical operations performed in the United States has been steadily increasing for the last five years. It is estimated that 228,000 weight-loss surgeries were performed in 2017. Of those, 59 percent were sleeve gastrectomy, 18 percent were gastric bypass, 3 percent were gastric band, and 1 percent were biliopancreatic diversion with duodenal switch. The remaining 14 percent were revisional procedures.

Complications following surgical treatment of severe obesity vary based upon the procedure performed and can be as high as 40 percent. Due to the high surgical volume, improving the safety of these operations has become a high priority, leading to the development of strict criteria for center accreditation, guidelines for safe and effective bariatric surgery, and careful monitoring of surgical outcomes.

This topic will review the major late complications of bariatric surgery. A description of bariatric procedures, indications and preoperative management, short-time medical outcomes, and long-term complications of laparoscopic operations are reviewed as separate topics.

LATE COMPLICATIONS

Complications of bariatric surgery that occur after 30 days include cholelithiasis, nutritional deficiencies, and neurologic and psychiatric complications. These will be discussed in the context of specific procedures below.

COMPLICATIONS OF SPECIFIC BARIATRIC PROCEDURES

Roux-en-Y gastric bypass — RYGB involves the creation of a small gastric pouch and an anastomosis to a Roux limb of jejunum that bypasses 75 to 150 cm of small bowel, thereby restricting food and limiting absorption. This procedure is one of the most common weight-loss procedures performed. Complications of RYGB are diverse and vary based upon the specific technique. Some complications are relatively specific to the surgical approach (open versus laparoscopic). Certain complications are seen during the early postoperative periods, while others may present weeks to months following the surgery.

Gastric remnant distension — Gastric remnant distension is a rare but potentially lethal complication following gastric bypass. The gastric remnant is a blind pouch and may become distended if paralytic ileus or distal mechanical obstruction occurs postoperatively. Iatrogenic injury to vagal fibers along the lesser curvature may also contribute, possibly by leading to impaired emptying of the bypassed stomach. Progressive distension can ultimately lead to rupture, spillage of massive gastric contents, and subsequent severe peritonitis. The combination of the large size of inoculum (liters) and the injurious contents (acid, bile, pancreatic enzymes, and bacteria) makes this complication much more serious than leakage occurring at the gastrojejunostomy.

Clinical features include pain, hiccups, left upper quadrant tympany, shoulder pain, abdominal distension, tachycardia, or shortness of breath. Radiographic assessment may demonstrate a large gastric air bubble.

Treatment consists of emergent operative decompression with a gastrostomy tube or percutaneous gastrostomy. Immediate operative exploration and decompression are required if percutaneous drainage is not feasible, or if perforation is suspected. Although gastrostomy is not performed routinely by most surgeons at the initial gastric bypass operation, drainage of the gastric remnant can prevent this rare but sometimes fatal complication. Routine gastrostomy should be considered in the elderly, super-obese patients, patients with diabetic gastropathy, and as part of revisional surgeries where gastric emptying may be delayed.

Stomal stenosis — Stomal (anastomotic) stenosis has been described in 6 to 20 percent of patients who have undergone RYGB. The etiology is uncertain, although tissue ischemia, marginal ulcer, or increased tension on the gastrojejunal anastomosis is believed to have a role. The stomal stenosis rate is higher in LRYGB and may be related to the use of the small-diameter (21 mm) circular staplers.

A stomal stenosis manifests clinically when the anastomosis narrows to a diameter of <10 mm. Patients typically present several weeks after surgery with nausea, vomiting, dysphagia, gastroesophageal reflux, and eventually an inability to tolerate oral intake, including liquids. The diagnosis is usually established by endoscopy or with an upper gastrointestinal series.

Endoscopic balloon dilation is usually successful. The stoma should be dilated to a diameter of approximately 15 mm; further dilation to 20 mm may reduce the restrictive effect of RYGB. The gastrojejunal (GJ) anastomosis should not be dilated by >3 to 4 mm at a time, and, as such, most patients will need two to three endoscopic procedures to reach a 15 mm anastomosis. The complication rate for dilation is approximately 3 percent. Careful communication between

the endoscopist and the surgeon regarding the details of the original operation is important to minimize the risk of endoscopic complications.

Patients with a chronic stenosis that is refractory to multiple dilations require a surgical revision of the GJ anastomosis after a delay of a few months to allow the gastric pouch to dilate. Fortunately, <0.05 percent of patients require such a revision surgery.

Marginal ulcers — Marginal ulcers have been reported in 0.6 to 16 percent of patients. Marginal ulcers occur near the gastrojejunostomy and result from acid injuring the jejunum, or they can be associated with a gastrogastric or, rarely, gastrocolic fistula.

Causes of marginal ulcers include:

- Poor tissue perfusion due to tension or ischemia at the anastomosis
- Presence of foreign material, such as staples or nonabsorbable suture
- Excess acid exposure in the gastric pouch due to gastrogastric fistulas
- Nonsteroidal anti-inflammatory drug use
- *Helicobacter pylori* infection
- Smoking

Patients with marginal ulcers can present with nausea, abdominal pain, gastrointestinal bleeding, stomal stenosis, or perforation. The diagnosis of a marginal ulcer is established by upper endoscopy.

Initial medical treatment consists of gastric acid suppression with a six-week course of proton pump inhibitors, with or without the addition of sucralfate, followed by a repeat endoscopy to ensure healing. During the follow-up, nonsteroidal anti-inflammatory drugs should be discontinued, and patients should be encouraged to stop smoking. An upper gastrointestinal series or a computed tomography (CT) scan with oral contrast should be performed to rule out a gastrogastric fistula.

The prevalence of *H. pylori* infection in patients undergoing weight loss surgery is high, and a significant proportion of them have postoperative foregut symptoms. Observational studies have shown that patients with *H. pylori* colonization have a higher incidence of marginal ulcer formation. Furthermore, in one study, preoperative testing and treatment of *H. pylori* significantly reduced the incidence of postoperative marginal ulcers (2.4 versus 6.8 percent in unscreened patients).

Although medical management of marginal ulcers is successful in 85 to 95 percent of patients, surgery may be indicated if marginal ulcers perforate or if persistent pain or recurrent bleeding occurs despite maximal medical therapy. In stable patients, revision of the gastrojejunostomy with truncal vagotomy should be performed. In unstable patients, a Graham patch can be used to seal any perforation, the local area washed out, and a feeding tube placed. If stenosis occurs, the GJ anastomosis can be revised at a later time when the patient is more stable.

Candy cane Roux syndrome — Candy cane Roux syndrome in patients who have undergone RYGB refers to an excessively long blind afferent Roux limb at the gastrojejunostomy causing postprandial pain often relieved by vomiting. It is believed that the blind afferent limb ("candy cane") acts as an obstructed loop when filled with food (often preferentially), and the distention of the loop causes pain until the food either spills into the Roux limb or is vomited back out.

Patients have been reported presenting as early as three months and as late as 11 years after their initial RYGB, typically with symptoms of postprandial epigastric pain, nausea, vomiting, and reflux or food regurgitation. The diagnosis is confirmed by upper gastrointestinal contrast studies or endoscopy. On upper gastrointestinal series, the afferent limb fills before contrast spills into the Roux limb. On upper endoscopy, the afferent limb is usually the most direct outlet of the gastrojejunostomy.

The treatment is revision bariatric surgery, most commonly laparoscopic resection of the afferent limb, which ranged in length from 3 to 22 cm in one study (mean of 7.6 cm). Symptoms resolve after revision surgery in most patients. Surgeons should minimize the length of the blind afferent loop left at the time of initial RYGB to prevent candy cane Roux syndrome.

Cholelithiasis — Cholelithiasis develops in as many as 38 percent of patients within six months of surgery, and up to 41 percent of such patients become symptomatic. Rapid weight loss can also contribute to the development of gallstones by increasing the lithogenicity of bile. The high frequency of cholelithiasis can be reduced to as low as 2 percent with a six-month course of ursodeoxycholic acid (UDCA; ursodiol, a synthetic bile salt) given prophylactically after weight-loss surgery.

The decision to perform a cholecystectomy at the time of bypass is controversial. Some surgeons recommend performing cholecystectomy at the time of bypass if a patient has symptomatic gallstones preoperatively. The surgical

opinion about asymptomatic gallstones is more divided, and studies have failed to demonstrate a benefit for simultaneous cholecystectomy for incidental gallstones at the time of RYGB.

Patients can also develop choledocholithiasis (stones in the common bile duct), which can be difficult to treat in the postoperative RYGB patient. Diagnosis of choledocholithiasis can be confirmed by ultrasound or magnetic resonance cholangiopancreatography (MRCP); however, endoscopic intervention and management can be difficult because of the relative inaccessibility to the duodenum due to the altered anatomy of the Roux-en-Y configuration. As a result, successful endoscopic retrograde cholangiopancreatography (ERCP) with cannulation of the papilla is very difficult to perform. Thus, treatment of choledocholithiasis may require surgery or transhepatic percutaneous access. Alternatively, placement of a gastrostomy tube into bypassed stomach at the time of gastric bypass, with the addition of a radiopaque marker to facilitate future percutaneous access to the gastric remnant, has also been described. Surgical gastrostomy for pancreatobiliary and duodenal access following RYGB has been done with good results and may be an option when traditional endoscopic approaches are impossible.

Ventral incisional hernia — Ventral incisional hernias occur with a frequency of 0 to 1.8 percent in laparoscopic series and as high as 24 percent in open series, underscoring a clear advantage of the laparoscopic approach in this regard.

Incisional hernias present with an enlarging bulge, pain, or obstructive symptoms. Severe obesity is associated with increased intra-abdominal pressure and thus a high risk of hernia development after a laparotomy. Many surgeons postpone a formal repair until significant weight loss occurs (>1 year). Indications for early surgical repair include significant pain, bowel obstruction, and rapid enlargement of the hernia.

Internal hernias — Mesenteric defects that are created during a Roux-en-Y gastric bypass include:

- A mesenteric defect at the jejunojejunostomy
- A space between the transverse mesocolon and Roux-limb mesentery (ie, Petersen's defect)
- A defect in the transverse mesocolon in patients with a retrocolic Roux-limb

Internal hernias have been described in 0 to 5 percent of patients after laparoscopic gastric bypass. To reduce the incidence of internal hernias, all mesenteric defects should be closed with nonabsorbable sutures. In a multicenter trial, 2507 patients were randomly assigned to undergo laparoscopic Roux-en-Y gastric bypass with or without mesenteric defect closure. Compared with nonclosure, mesenteric closure significantly decreased the incidence of reoperation due to small bowel obstruction (6 versus 10 percent at three years) but increased early postoperative complications due to kinking of the jejunojejunostomy (4.3 versus 2.8 percent). In another study, the small bowel obstruction rate was reduced from 6 to 3 percent when all such defects were routinely closed.

The majority of internal hernias after laparoscopic gastric bypass occurred through the transverse mesocolon defect (44 of 66 in one study). The use of an antecolic Roux limb can, in theory, reduce the risk of internal hernia formation by eliminating the transverse mesocolic defect. A 2016 meta-analysis found that the use of an antecolic Roux limb, as opposed to a retrocolic Roux limb, was associated with lower rates of postoperative internal hernia (1.3 versus 2.3 percent) and small bowel obstruction (1.4 versus 5.2 percent). However, the two techniques have not been directly compared with each other in randomized trials.

Internal hernias can be difficult to detect radiographically because they are intermittent. Several studies have shown that the "mesenteric swirl" sign on CT scan is the best indicator of an internal hernia following gastric bypass. The mesenteric swirl sign shows a swirled appearance of mesenteric vessels or fat at the root of the mesentery. The mesenteric swirl sign has high sensitivity (78 to 100 percent) and specificity (80 to 90 percent) and can be easily recognized by experienced radiologists with high interobserver agreement.

Small bowel obstruction — Small bowel obstruction (SBO) can occur at any time after an RYGB, with a lifetime incidence of 3 to 5 percent. Post-RYGB SBO is most commonly caused by herniation of small intestine through one of the mesenteric defects (ie, internal hernias), which are discussed separately. Alternatively, SBO can also be caused by adhesive disease, an incisional hernia, or intussusception (typically at the jejunojejunal [JJ] anastomosis).

Patients with SBO can present acutely or subacutely with vague, intermittent, crampy, and sharp abdominal pain usually unrelated to eating. Symptomatic patients should undergo CT scan, and those who are diagnosed with SBO due to internal hernia by CT scan should undergo urgent surgical exploration to reduce the hernia. SBO due to internal hernia is likely be a closed loop obstruction, which has a higher perforation risk. An uncorrected SBO due to internal hernia could lead to bowel strangulation, which may necessitate extensive bowel resection and could result in short bowel syndrome.

If the CT scan is normal but patients continue to have symptoms suggestive of SBO, they should be explored laparoscopically to exclude an internal hernia or other cause of a SBO.

Short bowel syndrome — RYGB and other bariatric procedures can be complicated by short bowel syndrome (SBS) that results from small bowel resections for internal hernias or bowel obstruction from adhesions. In a retrospective

review of 265 patients, 11 developed SBS following bariatric surgery. In some cases, this complication may require intestinal transplantation.

Dumping syndrome — Dumping syndrome can occur in up to 50 percent of post-gastric bypass patients when high levels of simple carbohydrates are ingested. In a Danish survey of 1429 patients who underwent RYGB, 9.4 and 6.6 percent reported experiencing moderate-to-severe symptoms indicative of early dumping and hypoglycemia, respectively. In that cohort, the total prevalence of one or both types of symptoms was 12.6 percent (95% CI 10.9 to 14.4 percent); Patients who are younger than 35 years of age or have a body mass index (BMI) <25 kg/m^2 were more likely to be symptomatic than older or more obese patients.

There are two types of dumping syndrome, early and late.

Early dumping syndrome – Early dumping syndrome has a rapid onset, usually within 15 minutes. It is the result of rapid emptying of food into the small bowel. Due to the hyperosmolality of the food, rapid fluid shifts from the plasma into the bowel occur, resulting in hypotension and a sympathetic nervous system response. Patients often present with colicky abdominal pain, diarrhea, nausea, and tachycardia.
Patients should avoid foods that are high in simple sugar content and replace them with a diet consisting of high fiber, complex carbohydrate, and protein rich foods. Behavioral modification, such as small, frequent meals, and separating solids from liquid intake by 30 minutes, are also advocated. Usually, early dumping is self-limiting and resolves within 7 to 12 weeks.

Late dumping syndrome – Late dumping syndrome, currently referred to as postprandial hyperinsulinemic hypoglycemia (PHH), is a rare complication of bariatric surgery. It occurs in 0.1 to 0.3 percent of patients, most commonly after RYGB. Symptoms of PHH, including dizziness, fatigue, diaphoresis, and weakness, usually occur one to three hours after ingestion of a carbohydrate-rich meal, typically months to years after surgery, and are associated with documented hypoglycemia. The pathophysiology of PHH is not fully understood but likely includes alterations in multiple hormonal and glycemic patterns (eg, increase in incretin levels). Most patients with PHH can be managed with the same dietary modification suggested above for early dumping syndrome. Patients refractory to dietary modification can be treated with medications (eg, nifedipine, acarbose, diazoxide, or octreotide), gastrostomy tube feeding into the remnant stomach, or revisional bariatric surgery. Pancreatic resection has unproven benefit and should not be performed for PHH.

Dumping may contribute to weight loss in part by causing the patient to modify his or her eating habits.

Metabolic and nutritional derangements — Metabolic and nutritional derangements are common in severely obese patients and can be exacerbated following after bariatric surgery, making postoperative life-long compliance with appropriate dietary choices and vitamin supplementation imperative. Decreased oral intake as well as altered absorption of food from the stomach and small bowel reduces absorption of various micronutrients, particularly iron, calcium, vitamin B12, thiamine, and folate.

Hyperoxaluria and nephrolithiasis have been reported following Roux-en-Y gastric bypass surgery.

Hyperammonemic encephalopathy — Hyperammonemic encephalopathy has been reported in patients who are failing to thrive after complicated gastrointestinal surgeries that can include RYGB. The underlying etiologies are incompletely understood but include both genetic (eg, proximal urea cycle disorders) and nongenetic causes (eg, splenorenal shunt). The typical clinical features include hypoalbuminemia, hypoglycemia, low plasma zinc level, and other nutritional deficiencies.

The key to diagnosis is the early assessment of plasma ammonia levels in such patients with normal hepatic function but characteristic symptoms of encephalopathy. Once hyperammonemic encephalopathy is diagnosed, it can be treated with supportive and medical care to reduce ammonia levels.

Nephrolithiasis and renal failure — RYGB has been linked to metabolic changes that could alter urine chemistry profiles, resulting in both higher calcium oxalate supersaturation and urine oxalate, lower citrate, and lower volume. Consequently, patients have a higher risk of developing nephrolithiasis after RYGB (pooled relative risk 1.79, 95% CI 1.54-2.10).

While uncommon, increased absorption of calcium oxalate could also lead to deposition in the renal parenchyma, resulting in oxalate nephropathy and renal failure. A retrospective review of 11 patients with oxalate nephropathy found that all were hypertensive and nine were diabetic before the procedure. Renal biopsies revealed diffuse tubular degenerative changes, abundant tubular calcium oxalate deposits, and varying degrees of tubulointerstitial scarring.

Postoperative hypoglycemia — A small number of patients develop blackouts and seizures after weight-loss surgery due to a severe form of recurrent hyperinsulinemic hypoglycemia. Pancreatic nesidioblastosis has been proposed as a mechanism for the pathologic finding of beta islet hypertrophy in these patients, although a few cases of insulinomas have been found. Gastric-bypass-induced weight loss may unmask an underlying beta cell defect or contribute to pathological islet hyperplasia.

A wide variety of clinical approaches have been proposed to address severe hypoglycemia after gastric bypass. We suggest beginning with simpler and safer interventions:

- Most patients with symptomatic hypoglycemia respond well to dietary modification (low carbohydrate diet). Those patients who are refractory to a low carbohydrate diet can be treated with the alpha-glucosidase inhibitor acarbose.
- Based on the theory that severe, disabling hypoglycemia after gastric bypass surgery occurs in a subset of patients with loss of gastric restriction, with resultant rapid food passage and absorption, restoration of gastric restriction can result in symptom resolution. Gastric restriction can be restored by surgical placement of a silastic ring or an adjustable gastric band around the pouch. In one series, symptoms resolved in 11 of 12 patients with this approach.
- Subtotal pancreatectomy or total pancreatectomy has been recommended by some surgeons to control hypoglycemia. This should be reserved for patients who are refractory to less radical interventions.

Change in bowel habits — Loose stool and diarrhea are more common after BPD and RYGB. Constipation is more common after gastric banding. In a study of 290 severely obese patients undergoing bariatric surgery, 126 underwent RYGB, BPD was performed in 103 patients, and 61 patients had gastric banding. After RYGB, the proportion of patients with loose stools, diarrhea, or frequent flatus increased significantly (46 versus 8 percent preoperatively). After BPD, 55 percent of the patients reported an increase in loose stools or diarrhea or frequent flatus versus 8 percent preoperatively. Conversely, after gastric banding, 39 percent of patients complained of constipation.

Steatorrhea and more frequent stools can occur with excessive fat intake. In addition, these symptoms can be due to subclinical lactose intolerance, which is only recognized when dairy products are used in an effort to achieve adequate protein intake after bariatric surgery.

Gastrogastric (GG) fistula — A gastrogastric fistula is a channel that develops between the gastric pouch and the excluded stomach remnant, allowing ingested food to enter the bypassed foregut (stomach and duodenum). GG fistulas occur in approximately 1 to 2 percent of patients after RYGB and most commonly cause marginal ulcers or weight regain.

In the early days of gastric bypass, surgeons stapled the stomach without completely dividing the gastric remnant from the pouch. The gastric pouch and gastric remnant stapled in continuity was associated with a 49 percent rate of gastrogastric fistula. The introduction of complete transection of these two segments has decreased the rate of gastrogastric fistula to 0 to 3 percent.

When persistent marginal ulcers or significant weight regain is seen in a post-RYGB patient, particularly in the setting of recurrent or new-onset gastroesophageal reflux symptoms, an upper gastrointestinal series or a CT scan with oral contrast should be performed to exclude a gastrogastric fistula as a cause. Patients diagnosed with a GG fistula who also have either significant weight regain or persistent symptoms from marginal ulcers (eg, abdominal pain, stomal stenosis, or gastrointestinal bleeding) are candidates for revision or repair.

Endoscopic techniques, including clipping, suturing, and stenting, have been used to treat GG fistula causing weight regain, but results are varied at best and recurrence rates are high. Surgical revision is probably the best option for patients with persistent pain, bleeding, or stenosis from a GG fistula. Although revisional bariatric surgery is generally riskier than primary procedures, acceptable complication rates as low as 22 percent have been achieved in experienced hands [14].

In preparation for dividing the GG fistula, the gastric pouch should be fully mobilized, and the path of the Roux limb should be outlined with an orogastric tube or endoscope. The GG fistula can be resected by stapling, in which case one must staple inside the previous staple line to avoid creating a blind pouch. Alternatively, the gastric remnant can be opened to allow the fistula to be accessed from the distal side. Once the anatomy is defined, a revision of the GJ anastomosis is performed. Following revisional bariatric surgery, drains and a feeding tube should be placed.

Failure to lose weight and weight regain — Failure to lose weight following Roux-en-Y gastric bypass is rare and is often due to maladaptive eating patterns during the early postoperative period. By contrast, significant late weight regain occurs in up to 20 percent of patients, especially those with super-obesity (body mass index [BMI] >50 kg/m^2) at the time of the initial operation. It is often due to progressive noncompliant eating and other behavioral habits, development of a functional GG fistula, gradual enlargement of the gastric pouch, or dilatation of the gastrojejunal anastomosis.

A GG fistula can cause weight regain by allowing food passage into the remnant stomach, thereby decreasing the restrictive effect of RYGB. The diagnosis and treatment of GG fistulas has been discussed above.

Dilatation of the gastric pouch or the gastrojejunal anastomosis may be responsible for weight gain in other patients. The stretched pouch and/or the outlet are thought to arise from repeated overdistension due to excessive food intake. These patients usually do not benefit from the high-risk revisional surgery. However, less invasive endoscopic procedures aimed at suture reduction of the pouch size or tightening of the stoma have been successful, at least with

short-term follow-up. The long-term efficacy of these therapies is not known and is being formally assessed as part of a clinical trial.

Gastric banding — Gastric banding (GB) is a purely restrictive procedure that involves placement of an adjustable silicone device at the gastric cardia near the gastroesophageal junction, limiting the amount of food consumed. Restriction can be adjusted by injecting saline into a subcutaneous port connected to the band.

GB is the third most common weight-loss surgery performed in the United States. GB has the lowest mortality rate among all bariatric procedures. The Australian Safety and Efficacy Register of New Interventional Procedures reported three deaths out of 5827 gastric banding procedures (0.05 percent).

However, GB has been associated with several complications. An initial trial of GB in the United States showed disappointing weight loss outcomes and high complication rates, associated with relatively high revisional surgery rate (40 percent). Following changes in the surgical technique, subsequent trials in Europe, Australia, and the United States have shown fewer complications. Long-term results from a series of 78 GB patients showed that nearly 40 percent of patients experienced major complications, 22 percent had minor complications, and almost half of the patients required reoperation. Major complications included pouch dilation (11 percent), band erosion (28 percent), and band infection (1 percent). Minor complications included incisional hernias (5 percent), port-tubing disconnections (20 percent), and port infections (2 percent).

Late complications of GB include band erosion, band slippage or prolapse, port or tubing malfunction, leakage at the port site tubing or band, pouch or esophageal dilatation, and esophagitis. Almost 50 percent of patients will need surgical revision or removal of the band. Failed bands (due either to complications or inadequate weight loss) can generally be converted to other bariatric procedures such as RYGB, sleeve gastrectomy, or a duodenal switch.

In addition, the rate of long-term complications and rates of reoperation are higher with laparoscopic adjustable gastric banding (LAGB) compared with RYGB. In a prospective study of 442 patients matched for age, gender, and BMI, patients undergoing LAGB had a significantly higher rate of long-term complications compared with patients undergoing RYGB (41.6 versus 19.0 percent). Patients undergoing LAGB also had a higher rate of reoperation at six years of follow-up (26.7 versus 12.7 percent).

Stomal obstruction — Acute stomal obstruction is an early complication that can occur in up to 14 percent of GB patients. Obstruction is usually caused by inclusion of excess perigastric fat, use of a band of insufficient diameter for the thickness of the tissue, or significant tissue edema. Patients usually present with persistent nausea, vomiting, and inability to tolerate secretions or oral intake. The diagnosis is confirmed with an upper gastrointestinal series demonstrating no passage of contrast beyond the band.

Acute stomal obstruction due to edema can initially be treated conservatively with nasogastric tube decompression until the edema subsides, although a potential for aspiration pneumonia and stomach ischemia exists. Persistent obstruction requires surgical revision or removal of the band. Meticulous removal of excess perigastric fat at the time of initial band placement may help prevent this complication. The use of larger-diameter bands may also help to reduce the incidence of acute postoperative obstruction.

Port infection — Port infection has been reported in 0.3 to 9 percent of GB patients. Because the port is a foreign body, port infection is treated with surgical removal, especially in association with band erosion. Overall, the incidence of port site infection ranges from 0.3 to 9 percent. If an isolated port infection is found, the infected port is removed and a new port is reimplanted once the infection clears.

Band erosion — Band erosion through the wall of the stomach has been reported in up to 7 percent of GB patients, and it is thought to occur as a result of either gastric wall ischemia from an excessively tight band, mechanical trauma related to the band buckle, or thermal trauma from electrosurgical energy sources used during band placement. Band erosion is a late complication and occurs at a mean of 22 months after surgery. Introduction of new band technology and placement technique is likely to result in a reduction of band erosions.

Clinical signs of band erosion include infection, failure of weight loss, or nausea and vomiting. Epigastric pain and hematemesis can also signal erosion of the lap band into the left gastric artery. This can happen when the lap band erodes into the posterior part of the stomach near the cardioesophageal junction. This complication can be avoided by careful placement during the initial surgery, making sure not to include the ascending branch of the left gastric artery during band placement.

Band erosion can be diagnosed by endoscopy, and treatment involves removal of the band, which can be done laparoscopically. Successful endoscopic removal has also been reported when the buckle of the band is visible endoscopically. It is generally recommended that revision to another bariatric procedure be delayed for at least two to three months after an episode of band erosion, as the complication rate with immediate revision is increased.

Band slippage and gastric prolapse — Band slippage involves prolapse of part of the stomach through the band, with varying degrees of gastric obstruction.

- Anterior prolapse involves migration of the band cephalad, which creates an acute angle with the stomach pouch and esophagus, resulting in obstruction.
- Posterior gastric prolapse occurs when the stomach migrates cephalad, displacing the band caudally and creating a new pouch.

Slippage rates were as high as 24 percent in the initial FDA trial but were lower (2 to 14 percent) in subsequent studies. An early technique (involving perigastric dissection with placement of a Lap-Band directly on the stomach wall) was associated with frequent gastric prolapse. The modern technique (via pars flaccida without exposure of the stomach wall) has decreased this complication significantly.

Anterior band fixation by gastro-gastric sutures is commonly performed to prevent band slippage. In a randomized trial of 706 patients who underwent LAGB in France, patients who had band fixation required fewer reinterventions (11 versus 19 percent) at three years in part because of a reduced band slippage rate (4 versus 10 percent). This trial also showed that patients with a baseline BMI <40 kg/m^2 were more likely to experience band slippage compared with those with a greater BMI (odds ratio 2.8, 95% CI 1.4-5.6).

Gastric prolapse is characterized by food intolerance, epigastric pain, and acid reflux. Diagnosis is confirmed with an upper gastrointestinal series demonstrating either malposition of the band or dilatation and prolapse of the gastric pouch.

Surgery is required urgently or emergently, depending on the presentation. Repair of the prolapse can sometimes be accomplished by repositioning the band, but often the band needs to be replaced or removed altogether, especially if significant inflammation is found.

Port malfunction — Port malfunction results if the tubing disconnects, subcutaneous port flips, or leakage within the system occurs. Such problems lead to inability to titrate the instilled volume of saline in the system. Reported incidence of port and tubing malfunction ranges from 0.4 to 7.0 percent. These problems usually become evident as an inability to access port and maintain band volume, or the development of weight gain. These complications require surgical repair or exchange of the hardware to attain band adjustability. Port dislocation can be reduced by attaching the port to a broad surface mesh first before anchoring to the rectus fascia.

Esophagitis — Esophagitis and reflux are infrequent complications following Lap-Band. Deflation of the band and acid-suppression therapy are the mainstays of treatment. However, if intractable to medical therapy, band removal or conversion to other procedure such as RYGB may be necessary.

Esophageal dilatation — Esophageal dilatation proximal to the band device has been observed in as many as 10 percent of patients. This so-called "pseudoachalasia syndrome" may develop when the band is excessively inflated or in the setting of excessive amounts of food intake. Pouch dilatation has also been associated with a history of binge eating behavior. Patients often present with food and saliva intolerance, reflux, and epigastric discomfort. The diagnosis can be confirmed with an upper gastrointestinal series.

The initial treatment should be removal of all the fluid from the band and behavioral diet modifications. This is usually successful in reversing esophageal dilatation. However, persistent dilatation may require replacement of the band in a new location on the stomach or conversion to a different procedure.

Deflation of the band alone is usually successful in reversing esophageal dilatation. However, persistent dilatation may require replacement of the band to a new location on the stomach or conversion to a different procedure.

Hiatus hernia — Hiatus hernia is often a preexisting but unrecognized condition in patients undergoing bariatric surgery**.** This can lead to ongoing intractable reflux necessitating reoperation or band removal. Thus, a simple crural repair can be performed at the initial operation to avoid these complications. A retrospective review of 1298 patients who underwent GB alone and 520 patients who underwent GB with concurrent hiatal hernia repair showed that the rate of reoperation was significantly reduced in patients who had hiatal repair at the time of GB as compared with those who had GB alone (1.7 versus 5.6 percent, respectively).

Sleeve gastrectomy — Laparoscopic sleeve gastrectomy (SG) is a restrictive procedure initially developed as part of a staged approach for high-risk super-obese patients. SG is increasingly being performed as a standalone operation with good weight loss and resolution of obesity-related comorbidities. A study of 14,776 sleeve gastrectomies confirmed that SG was intended as the sole operation in 86.3 percent of the procedures. In 2013, sleeve gastrectomy surpassed gastric bypass as the most commonly performed weight loss surgery in the United States.

Sleeve gastrectomy involves creating a "sleeve" of stomach over a bougie and removes a large portion of the greater curvature of the stomach, leaving a small tube along the lesser curvature. SG also produces a decrease in ghrelin levels for up to a year, which may reduce the desire for food.

Significant advantages of SG include low complication (3 to 24 percent) and mortality (0.39 percent) rates, the ease of performing the procedure, preservation of the pylorus, maintenance of physiological food passage, and the avoidance of foreign material.

The most common complications of SG include bleeding, narrowing or stenosis of the stoma, and leaks:

Bleeding — Bleeding can occur from the gastric or short gastric vessels during dissection of the greater curve. Most of the bleeding problems associated with SG occur from the staple line after transection of the stomach. The bleeding is most likely a result of the large staples used for the thick tissue in the distal stomach. Large staples are not adequate to seal small vessels. This has led many surgeons to reinforce the staple line by over-sewing, buttressing, or both.

Stenosis — Narrowing or stenosis can create gastric outlet obstruction. The presentation varies depending on the severity of the obstruction and can include dysphagia, vomiting, dehydration, and the inability to tolerate an oral diet. The gastroesophageal junction and the incisura angularis are the two most common areas where stenosis occurs, and this can be diagnosed by an upper gastrointestinal series.

The most common reasons for the development of narrowing or stenosis are over-sewing the staple line and using a bougie that is too small. The preferable bougie size is currently debated in the literature and can range from 30 to 60 French. In most cases, surgeons use a 36 to 40 French bougie for the sleeve construction, and the larger sizes of bougies are reserved for when SG is being performed as part of a staged procedure.

Management of stenosis primarily consists of endoscopic dilation. If the area of stenosis is too long, surgical intervention may be necessary with conversion to a, RYGB, gastric stricturoplasty, or resection with gastrogastrostomy.

Gastric leaks — Gastric leaks after SG are one of the most serious complications and can occur in up to 5.3 percent of patients.

Most leaks are due to local factors at the site of the staple line, such as inadequate blood supply and oxygenation, which impede the healing process. Leaks can also be due to gastric-wall heat ischemia, a consequence of the heat generated by the cautery used during dissection of the greater curve. Although the blood supply to the stomach is robust, the gastroesophageal junction tends to be an area of decreased vascularity and thus more prone to leaks. Additionally, the stomach tends to be thinner at the angle of His, and some authors suggest that the large staple height used by many surgeons may not adequately seal this area of the stomach. Some surgeons recommend leaving a small portion of stomach distal to the angle of His and then imbricating with a running silk suture. However, clinical studies have not provided evidence that reinforcing the suture line decreases the rate of leak after sleeve gastrectomy.

Sleeve gastrectomy produces high intragastric pressure, which can affect the healing process and lengthen the amount of time for a leak to close.

Reoperation with primary repair during the early postoperative course is the best option for a leak following SG. Clinically stable patients may be able to undergo percutaneous drainage, antibiotic therapy, and parenteral nutrition until the leak is healed. Endoscopic therapy with the use of stents has also been employed for management of leaks, but migration of the stents has been a problem. Early diagnosis, adequate drainage, and gastric decompression are the mainstay of treatment for leaks.

Reflux — Gastroesophageal reflux after SG presents with classic symptoms such as burning pain, heartburn, and regurgitation. It can occur as an early and late complication. The first-line treatment is antireflux medical therapy. GERD unresponsive to antireflux medical therapy with no clear anatomic abnormalities, such as stoma stenosis or a hiatal hernia, can be effectively treated by conversion to RYGB.

Vertical banded gastroplasty — Vertical banded gastroplasty (VBG), also known as "stomach stapling," is a purely restrictive procedure involving creation of a small proximal gastric pouch lined by a vertical staple line and a tight prosthetic mesh.

The theoretical advantages of VBG include the relative simplicity of the procedure, and avoidance of rerouting of the gastrointestinal tract and associated malabsorption. The VBG has been largely supplanted by the RYGB, but patients who underwent VBG still present to bariatric surgeons today with complications including staple line disruption, stomal stenosis, band erosion, GERD, nausea/vomiting, marginal ulcers, and weight regain.

Staple line disruption — Disruption of the staple line results in a fistula to the fundus, which can lead to decreased restriction in the VBG. This complication can occur in 27 to 31 percent of the patients and can be as high as 48 percent if assessed on routine postoperative endoscopy. Staple line disruption typically leads to weight regain due to increased food consumption since patients can eat around their restriction without feeling full. Surgical treatment of this complication is conversion to an RYGB or a BPD.

Obstruction — Stomal stenosis occurs in approximately 20 to 33 percent and can occur due to fibrosis in the stomach or by the band itself. The resulting obstruction leads to food intolerance, reflux, and often weight regain due to dietary shifts to calorically dense liquids and softer foods. Staple line dehiscence, esophageal dilatation, and a fistula between the VBG pouch and occluded stomach have also been reported.

Stomal stenosis following VBG can initially be managed nonoperatively by endoscopic dilation, with surgery reserved for failures. However, dilation may be unsuccessful due to the rigid nature of the prosthetic band. A success rate of 68 percent for endoscopic dilation of stomal stenosis was described in one series. Symptomatic relief following endoscopic dilation is often short lived, and surgical revision may be necessary when symptoms persist. Dense scarring also presents a significant operative risk when revision is required.

Erosion of mesh band — Band erosion is a frequent late complication of VBG occurring with an incidence of 1 to 7 percent and usually occurs one to three years after the surgery. Patients generally present with abdominal pain and vomiting. Surgical removal is indicated if erosion is visualized by endoscopy.

Reflux — Gastroesophageal reflux after VBG presents with classic symptoms such as burning pain, heartburn, aspiration, and cough. It typically occurs as a late complication, as a result of stomal stenosis and pouch dilatation. GERD unresponsive to antireflux medical therapy often requires reversal of the VBG or conversion to RYGB. In a review of 25 patients undergoing a revision of a VBG for symptomatic reflux, esophagitis was present in 58 percent of patients and Barrett's esophagus in 28 percent.

Vomiting — Recurrent vomiting occurs in approximately 8 to 21 percent of patients following VBG. The etiology may be multifactorial, including maladaptive dietary patterns (such as eating too quickly or not chewing properly) as well as functional problems such as stomal stenosis, pouch dilatation, staple line disruption, or GERD. These patients will often become sweet eaters in an attempt to ingest calories in a form that does not cause vomiting.

Not all patients with recurrent vomiting require an operative revision. Initial treatment should consist of dietary modification (ie, proper chewing, eating at slower pace, and avoidance of problem foods that give recurrent vomiting) and radiologic and/or endoscopic evaluations for structural problems. Operative revision is required if the vomiting persists and leads to malnutrition and/or dehydration.

Biliopancreatic diversion and duodenal switch — Biliopancreatic diversion (BPD) is a malabsorptive procedure that relies limiting absorption of fats and starches to a relatively short segment of small intestine as well as decreasing the gastric reservoir size. BPD has not become widespread because of the technical complexity of the procedure with historically high surgical morbidity and mortality rates and concerns regarding the long-term nutritional outcomes, including significant protein calorie malnutrition, anemia, metabolic bone disease, and deficiencies of fat-soluble vitamins.

Biliopancreatic diversion differs from jejunoileal bypass in that no intestinal limb is excluded from flow, thus avoiding creation of a blind loop. Excellent weight loss results with morbidity and mortality rates comparable to RYGB have been described by the few centers that perform BPD along with its duodenal switch variant.

Jejunoileal bypass — Jejunoileal bypass (JIB) is a purely malabsorptive procedure popular in the 1960s and 1970s. The procedure produces significant weight loss by creating a surgical short bowel syndrome.

JIB is no longer used today because of a 50 percent morbidity rate and 10 percent mortality rate. Patients who previously underwent JIB should be followed carefully for signs of complications, particularly a deterioration in liver function. Studies have shown a high long-term complication rate, with a 21 percent rate of cirrhosis after 15 years.

Electrolyte imbalances — Over half of the patients who underwent JIB developed diarrhea and electrolyte imbalances, and these problems could persist more than five years after surgery. Arthritis, protein malnutrition, vitamin deficiencies, cirrhosis, nephrolithiasis with oxalate stones, and renal failure have also been associated with JIB.

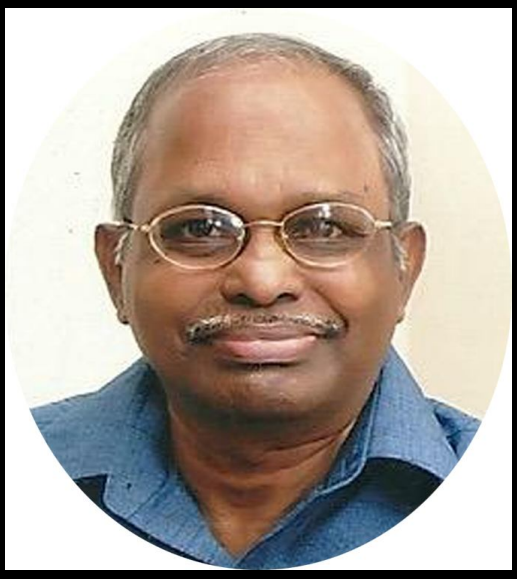
Renal failure — Increased absorption of calcium oxalate leads to deposition in the renal parenchyma. This can lead to a postobstruction nephropathy and renal failure, which has been described in up to 19 percent of patients. Conversion to a gastric bypass or reversal should be considered in patients with metabolic complications.

Cirrhosis — Hepatic abnormalities that may lead to cirrhosis can occur in up to 40 percent of patients and may persist or progress despite reversal in more than one third of patients. Some patients have progressed to decompensated cirrhosis requiring transplantation. If not already performed, reversal of the jejunoileal bypass at the time of transplant should be considered. Reversal prior to transplant may not be feasible because of the risk of precipitating hepatic decompensation in patients with advanced liver disease. Patients who do not undergo reversal at the time of transplant should be monitored closely, with reversal performed in those who develop progressive liver injury. Progressive liver injury appears histologically as increasing steatosis, lobular lymphocytic inflammation, pericellular fibrosis, Mallory bodies, and deranged architecture, all features resembling those seen in alcoholic liver disease.

SUMMARY AND RECOMMENDATIONS

- Roux-en-Y gastric bypass complications are diverse and include gastric remnant distension, stomal stenosis, marginal ulcer formation, cholelithiasis, ventral hernias, internal hernias, small bowel obstructions, hypoglycemia, dumping, metabolic and nutritional derangements, gastrogastric fistulas, and weight regain. Some complications are seen during the early postoperative periods while others may present weeks to months following the surgery.
- Laparoscopic adjustable gastric banding (LAGB) complications include acute stomal obstruction, band erosion, band slippage leading to gastric prolapse, port malfunction, esophageal dilatation, esophagitis, and infection.
- Laparoscopic sleeve gastrectomy complications include bleeding, narrowing or stenosis of the stoma, leaks, and reflux.
- Vertical banded gastroplasty complications include staple line disruption, stomal stenosis, band erosion, reflux, nausea/vomiting, marginal ulcers, and weight regain.
- Biliopancreatic diversion complications include significant protein calorie malnutrition, anemia, metabolic bone disease, and deficiencies of fat-soluble vitamins and vitamin B12.
- Jejunoileal bypass is no longer performed because of a high morbidity and mortality rate. However, patients who underwent this procedure can present years later with significant complications, including arthritis, protein malnutrition, vitamin deficiencies, cirrhosis, nephrolithiasis with oxalate stones, and renal failure.

OBITUARY



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PRINCIPLES OF CANCER IMMUNOTHERAPY

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INTRODUCTION

The fields of immunology and oncology have been linked since the late 19th century, when the surgeon William Coley reported that an injection of killed bacteria into sites of sarcoma could lead to tumor shrinkage. Since that time, exponential advances in the understanding of the intersection between immune surveillance and tumor growth and development have led to broad therapeutic advances that are now being studied in all cancer types.

The basic immunology and the various approaches to immunotherapy for tumors are discussed here. The details of immunology's role in specific malignancies are discussed in the relevant tumor-oriented topics, and the toxicity of checkpoint inhibitor immunotherapy is discussed separately.

TUMOR IMMUNOLOGY

Cell types involved in tumor recognition and rejection — An efficient and specific cytotoxic immune response against a tumor requires a complex, rapidly evolving interaction between various immune cell types in the adaptive and innate immune system.

- CD8+ lymphocytes and Th1/Th2 subclasses of CD4+ T lymphocytes, traditionally referred to as cytotoxic T cells and helper T cells. CD8+ and CD4+ lymphocytes initiate the distinction between self and non-self-antigens, through recognition at the "immune synapse."
- Natural killer (NK) cells do not require antigen presentation by the major histocompatibility complex (MHC) for cytotoxic activity. In fact, NK cells target cells with low MHC class 1 expression for destruction. Like T cells, NK cells express numerous inhibitory molecules as well, most notably various killer immunoglobulin-like receptor (KIR) subtypes.
- Additional cell types, such as FoxP3+ CD25+ CD4+ T regulatory (Treg) and myeloid derived suppressor cells (MDSCs) largely inhibit cytotoxic T lymphocyte activity. Th17 cells, subsets of CD4+ T cells that secrete interleukin (IL)-17, are implicated in autoimmunity and cancer.
- Macrophages differentiate into at least two different phenotypes: M1 macrophages, which release interferon (IFN) gamma and are responsible for phagocytosis, and M2 macrophages, which release cytokines such as IL-4, IL-10, transforming growth factor beta (TGF-beta), and dampen inflammatory responses and foster tolerance.

The "immune synapse" — The most widely studied phenomenon in immunologic surveillance is the ability of T lymphocytes to distinguish self- versus non-self-antigens, which are presented by antigen-presenting cells (APCs) such as dendritic cells. Overall, the cytotoxic activity of a CD8+ T cell is regulated by the presence and spatial orientation of a set of stimulatory and inhibitory receptors whose expression is regulated by a myriad of cytokines. Together, this configuration is often referred to as the "immune synapse"

The T cell receptor (TCR) complex consists of two major transmembrane components:

- The CD4 or CD8 receptor that binds to the MHC. The CD4/CD8 protein in most T cells consists of a highly variable alpha subunit linked to a beta subunit (ab). These variable regions of the CD4/CD8 molecule resemble the variable fragment (Fab) of an antibody and are responsible for the specificity of a specific T cell for a particular antigen.
- The CD3 molecule, which encodes a nonvariable transmembrane protein complex with an intracellular tyrosine-based activation component that relays surface signals to intracellular downstream effectors [7].

The TCR binds specific short stretches of amino acids presented by MHC molecules. MHC class 1 is expressed by all nucleated cells and is recognized by CD8+ T cells, while MHC class 2 molecules are constitutively expressed by APCs and are recognized by CD4+ T cells.

For efficient activation of a naïve CD8+ T cell, its TCR must bind to a peptide presented by the MHC in the presence of a second set of costimulatory signals. This interaction leads to CD3 intracellular signaling that causes secretion of pro-inflammatory cytokines such as IL-12 and IFN gamma. In the absence of a costimulatory signal, a state of peripheral tolerance to the antigen ("anergy") develops.

The most important costimulatory signal in naïve T cells is CD28, which binds to B7-1 and B7-2 (CD80/86) on the APC. This costimulatory process is tightly regulated by both "agonist" molecules (eg, GITR, OX40, ICOS) and inhibitory signals on both the APC and T cells, often collectively referred to as "immune checkpoint" molecules. Examples of co-inhibitory or "immune checkpoint" molecules include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death-1 (PD-1), TIM3, and LAG3. Chronic recognition of an antigen (such as that present in a malignant clone or in a chronic viral infection) may lead to feedback inhibition of effector T cell function, resulting in a phenotype termed "exhaustion".

Tumor evasion of immune surveillance — The prevailing theory of the immune system's influence on neoplastic progression is termed "cancer immunoediting," which proceeds in three phases:

- The elimination phase consists of innate and adaptive immune responses to specific tumor-associated antigens and is characterized by T, B, and NK cell effector function, which is mediated by cytokines such as IFN alpha, IFN gamma, and IL-12.
- The equilibrium phase is a balance between immune-mediated destruction by the adaptive immune system (eg, activated CD4+ and CD8+ T cells) and persistence of rare malignant clones.
- Immunologic escape describes the phase where malignant clones have acquired the ability to evade the adaptive immune system.

There are several posited mechanisms for escape from immune surveillance. Established mechanisms include:

- Loss or alteration of specific antigens or antigenic machinery. Tumors can lose major MHC class 1 expression or the intracellular machinery required to transport tumor antigens to the tumor surface for T cell recognition.
- Tumors can promote an immune-tolerant microenvironment by manipulation of cytokines (increased secretion of IL-6, IL-10, and TGF-beta; consumption of IL-2) that encourage infiltration of Treg cells, myeloid derived suppressor cells (MDSCs), and other cell types that inhibit cytotoxic T cell function. These cells can then actively suppress proliferation of CD4+ and CD8+ T lymphocytes that would otherwise recognize tumor antigens.
- Tumors can upregulate the expression of immune checkpoint molecules such as PD-1 and PD ligand 1 (PD-L1) that promote peripheral T cell exhaustion.
- Many oncogenic cell signaling pathways that were originally viewed as pure accelerators of cell division and growth are now understood to be mediators of immunologic escape. For example, constitutive KIT signaling in gastrointestinal stromal tumors leads to overexpression of indoleamine-2,3-dioxygenase (IDO), which enhances Treg infiltration that promotes tumor growth; this can be reversed in a CD8 T cell-dependent fashion with the KIT inhibitor, imatinib. Melanomas with beta-catenin/Wnt signaling inhibit dendritic-cell mediated antigen presentation and exclude CD8+ T cell infiltration.

Understanding these mechanisms of immunologic escape can suggest mechanisms for immune-based therapies that may be broadly applicable across cancer types.

THERAPEUTIC APPROACHESA number of therapeutic approaches are being studied to unleash the immune system and control malignancy. These approaches include cytokines, T cells (checkpoint inhibitors, agonism of costimulatory receptors), manipulation of T cells, oncolytic viruses, therapies directed at other cell types, and vaccines.

Cytokines — Initial approaches to immunotherapy harnessed the numerous downstream effects of cytokines and other substances that influence immune cell activity. Examples include:

- Interleukin (IL)-2 was initially discovered as T cell growth factor. IL-2 has pleiotropic effects on both cytotoxic T cell function as well as T regulatory (Treg) cell maintenance. The effects partially depend upon the dose and timing of IL-2 administration. At higher doses, IL-2 promotes CD8+ effector T cell and natural killer (NK) cytolytic activity and promotes differentiation of CD4+ cells into T helper (Th)1 and Th2 subclasses. At lower doses, IL-2 appears to preferentially expand Treg populations, probably due to the higher affinity of the trimeric IL-2 receptor (IL-2R, also known as CD25) on those cells, and inhibits the formation of Th17 cells implicated in autoimmunity. Although IL-2 use has been largely supplanted by the use of checkpoint inhibitors, bolus, high-dose IL-2 achieved durable objective responses in a minority of patients with melanoma and renal cell carcinoma (RCC), serving as proof of principle that the immune system could eliminate cancer cells.
- Lenalidomide and pomalidomide are immunomodulatory agents that have prolonged survival in multiple myeloma. These agents mediate their antitumor effects largely via the cereblon-mediated destruction of Ikaros family proteins that inhibit IL-2 secretion.
- Interferon (IFN) alfa-2b promotes Th1-mediated effector cell responses such as IL-12 secretion via STAT-1 and STAT-2-mediated downstream signaling events. IFN alfa has been used as adjuvant treatment of high-risk melanoma, although its long-term impact on overall survival is controversial; more recent data have demonstrated the role of immune checkpoint blockade as an adjuvant treatment with a likely better therapeutic index.
- Bacillus Calmette-Guerin (BCG), derived from attenuated mycobacterium bovis, induces a robust inflammatory response when injected in the bladder and is used for the treatment and secondary prevention of superficial bladder cancer.

Checkpoint inhibitors

PD-1 and PD ligand 1/2 — Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T cells, B cells, and NK cells. It is an inhibitory molecule that binds to the PD-1 ligand (PD-L1; also known as B7-H1) and PD-L2 (B7-H2). PD-L1 is expressed on the surface of multiple tissue types, including many tumor cells, as well as

hematopoietic cells; PD-L2 is more restricted to hematopoietic cells. The PD-1:PD-L1/2 interaction directly inhibits apoptosis of the tumor cell, promotes peripheral T effector cell exhaustion, and promotes conversion of T effector cells to Treg cells. Additional cells such as NK cells, monocytes, and dendritic cells also express PD-1 and/or PD-L1.

In general, PD-1 and PD-L1/L2 are upregulated in the context of pro-effector cytokines such as IL-12 and IFN gamma, highlighting their role as a physiologic brake on unrestrained cytotoxic T effector function. There are additional binding partners outside of the PD-1:PD-L1 axis; for example, PD-L1 has also been shown to inhibit CD80, suggesting layers of interaction between Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, and other pathways; these require further research to elucidate the context-dependent roles of each pathway in regulating T effector cell function.

Based upon prolonged overall survival in phase III trials and durable responses in phase II studies, antibodies inhibiting PD-1 (pembrolizumab, nivolumab) and PD-L1 (atezolizumab, avelumab, durvalumab) have been approved for a number of clinical indications and are being evaluated in multiple other malignancies; these are discussed in specific disease-related topics.

CTLA-4 — CTLA-4 was discovered in 1987 and implicated as a negative regulator of T cell activation in the mid-1990s. CTLA-4 exerts its effect when it is present on the cell surface of CD4+ and CD8+ T lymphocytes, where it has higher affinity for the costimulatory receptors CD80 and CD86 (B7-1 and B7-2) on antigen-presenting cells (APCs) than the T cell costimulatory receptor CD28. The expression of CTLA-4 is upregulated by the degree of T cell receptor (TCR) activation and cytokines such as IL-12 and IFN gamma, forming a feedback inhibition loop on activated T effector cells. As a result, CTLA-4 can be broadly considered a physiologic "brake" on the CD4+ and CD8+ T cell activation that is triggered by APCs.

CTLA-4 was initially implicated in immune surveillance of cancer when inhibition of CTLA-4 in mouse models of sarcoma and colon adenocarcinoma led to tumor shrinkage. The anti-CTLA-4 antibody ipilimumab was the first immune checkpoint inhibitor to be approved based upon its ability to prolong survival in patients with metastatic melanoma. Ipilimumab has also been approved as adjuvant therapy for high-risk melanoma as an alternative to IFN.

Tremelimumab, another CTLA-4-inhibiting monoclonal antibody, did not demonstrate a survival advantage over chemotherapy in patients with advanced melanoma, potentially related to inadequate dosing schedule. Additional trials with this antibody are ongoing to evaluate combinatorial approaches.

Other potential targets — Increased understanding of the underlying immunologic mechanisms is leading to the identification of several additional potential targets for checkpoint inhibition. Examples of these include the following, although all are currently only in early stage clinical development:

- **BTLA** – B and T cell lymphocyte attenuator (BTLA) is a ligand of herpes virus entry mediator (HVEM) whose interaction leads to decreased production of cytokines and cell proliferation by CD4+ T cells. It is expressed on B, T and NK cells as well as APCs. BTLA is induced during T cell activation, with persistent expression in TH1 but not TH2 cells. Blockade of BTLA has been shown to enhance NY-ESO-1 specific CD8+ T cell function and add to anti-PD-1 efficacy.
- **VISTA** – V-domain Ig suppressor of T cell activation (VISTA), as connoted by its name, shares homology with PD-L1 and is a negative checkpoint ligand. It is found in hematopoietic tissues and T cell-infiltrated structures, including tumors. VISTA blockade has been shown to increase T cell infiltration and function in tumors, thereby reducing tumor growth.
- **TIM-3** – T cell immunoglobulin and mucin domain 3 (TIM-3) is expressed by dendritic cells, monocytes, CD8 T cells, and T-helper-1 (Th1) cells. When TIM-3 binds galectin-9, its ligand that is often found on tumors, this causes TH1 cell death; conversely, TIM-3 blockade causes TH1 cell hyperproliferation and cytokine release. In combination with anti-CTLA4 or anti-PD-1, TIM-3 blockade led to tumor shrinkage in a mouse model.
- **LAG3** – Lymphocyte activation gene 3 (LAG3) is expressed by B cells, some T cells, NK cells, and tumor infiltrating lymphocytes (TIL). The LAG3 protein enhances Treg activity by binding major histocompatibility complex (MHC) class II and hampering T cell differentiation and proliferation. Dual LAG3 and PD-1 blockade shows preclinical efficacy. Preliminary data from a study combining an antibody targeting LAG3 and nivolumab found initial evidence of clinical activity in patients with advanced melanoma who had progressed on previous therapy with an antibody targeting PD-1.
- **CD47** – The antigen CD47 may be expressed on tumor cells, protecting them from phagocytosis by macrophages, and is therefore a potential target for anticancer therapy. In a phase Ib study of 22 heavily pretreated patients with relapsed or refractory non-Hodgkin lymphoma (NHL; 15 with diffuse large B cell lymphoma and 7 with follicular lymphoma), Hu5F9-G4 (a humanized anti-CD47 monoclonal antibody) in combination with rituximab was associated with objective responses in half, including complete response in more than one-third. Adverse events were generally mild. This study suggests that targeting CD47 may enhance the activity of tumor-directed antibodies in patients with NHL.

Agonism of costimulatory receptors — Multiple costimulatory receptors are involved in the immune response to tumors, and hence are potential targets for cancer immunotherapy. The following are either being studied in preclinical animal models or are in early phases of clinical development as noted:

- **4-1BB (CD137)** – 4-1BB is expressed on activated T cells, activated NK and NKT cells, as well as being expressed constitutively on some dendritic and Treg populations. When stimulated by 4-1BBL, its natural ligand, or agonist antibodies, this promotes activity of T cells, dendritic cells, monocytes, and neutrophils. Preclinical data show tumor control with agonist anti-4-1BB antibodies alone and in combination with other modalities. A 4-1BB agonist antibody urelumab (BMS-663513) was originally developed as monotherapy, but development was suspended due to fatal liver toxicity when given at higher doses. Urelumab is now being studied at lower doses both as monotherapy and in development with other agents. Another 4-1BB agonist antibody, PF-05082566, has also shown clinical activity in a phase I trial without toxicity at lower dose levels.
- **OX40 (CD134)** – OX40 is expressed on activated CD4+ T cells one to two days after activation, as well as on CD8+ T cells, dendritic cells, neutrophils, and Tregs. OX40 is stimulated by the OX40 ligand (OX40L) found on APCs and activated T cells. Interaction with an agonist antibody can also reverse regulatory T cells' suppressive function. In preclinical models, OX40 agonism has antitumor activity on its own and in combination with various other chemo- and immunotherapies. Studies of anti-OX40 and anti-OX40L antibodies are ongoing.
- **GITR (CD357)** – Glucocorticoid-induced tumor necrosis factor (TNF)-like receptor (GITR) expression increases on CD4+ and CD8+ T cells one to three days after stimulation and is then sustained. T cell proliferation and effector function, as well as prevention of activation-induced cell death (AICD), results from GITR stimulation. GITR may also play a role in leukocyte adhesion and transmigration. Furthermore, GITR can reverse suppression by Tregs, as well as induce memory, contributing to protection from tumor rechallenge in mouse models. Administration of the murine anti-GITR antibody DTA-1 impairs Treg function and improves antitumor activity of CTLs.
- **ICOS** – Inducible T cell co-stimulator (ICOS) is expressed on activated T cells and has multiple functions, including a role in isotype switching, germinal center formation, and effector and regulatory CD4+ T cell responses. ICOS ligand engagement of ICOS in combination with CTLA-4 blockade enhanced efficacy of the latter.
- **CD40** – CD40 is a costimulatory molecule present on APC and necessary for dendritic cell activation that binds its ligand, CD40L, expressed on T helper cells. Two agents, dacetuzumab and lucatumumab, have been studied in hematologic malignancies.
- **CD28** – CD28 is constitutively expressed on T cells and is a costimulatory receptor for CD80 (B7.1) and CD86 (B7.2). In a phase I trial in which CD28 was targeted by a monoclonal antibody, TGN1412, the six treated patients all suffered organ damage and critical illness secondary to cytokine release. CD28 is used as a stimulator of T cells ex vivo, but targeted antibodies are no longer under development due to toxicity.

Combination immune checkpoint blockade strategies — There currently are multiple clinical trials investigating combinations of various checkpoint inhibitors based upon the results with checkpoint inhibitors as monotherapy.

Concurrent CTLA-4 and PD-1 blockade is furthest along in clinical development. The combination of ipilimumab plus nivolumab has demonstrated a significantly higher response rate, progression-free survival, and overall survival than ipilimumab monotherapy in metastatic melanoma. Similarly, the combination of nivolumab plus ipilimumab has demonstrated an improved response rate, overall survival, and tolerability compared with sunitinib in patients with treatment-naïve advanced RCC. As expected, the rate of grade 3 or 4 adverse events was higher with combined ipilimumab plus nivolumab versus nivolumab or ipilimumab monotherapy.

Other clinical trials combining ipilimumab and nivolumab are underway in a multitude of other diseases. Durvalumab plus tremelimumab, another combination utilizing PD-L1 and CTLA-4 blockade, is also being investigated in multiple cancers.

Manipulating T cells — Adoptive T cell transfer broadly refers to the practice of manipulating patient-specific T cells ex vivo to make them more reactive to specific antigens.

Chimeric antigen receptors — Chimeric antigen receptor (CAR) T cells are genetically modified T cells, where a patient's own (autologous) T cells are manipulated ex vivo to express the antigen-binding domain from a B cell receptor that is fused to the intracellular domain of a CD3 TCR (CD3-zeta). As a result, recognition of a specific cell surface antigen activates T cell response independently of MHC recognition. Various modifications can enhance CAR effector function, such as co-expression of intracellular costimulatory domains such as CD28 or 4-1BB (CD137) or pro-effector cytokines such as IL-12.

CAR T cells have been studied most extensively in hematologic malignancies. Clinical trials targeting CD19, the pan-B cell antigen, have shown remarkable success in B cell acute lymphoblastic leukemia (B-ALL) and pre-B-cell ALL. Side effects are substantial in certain patients and include signs of the cytokine release syndrome such as fever, hypotension, altered mental status, and seizures, with some patients requiring intensive care. Trials in patients with chronic lymphocytic leukemia (CLL) have also shown promising results.

Numerous trials in hematologic malignancies are ongoing, with early development in some solid tumors targeting shared antigens such as CEA, mesothelin, and HER2.

Ex-vivo expansion of tumor-infiltrating lymphocytes — Tumor-infiltrating lymphocytes (TILs) represent an immune cell population that recognizes tumor antigen but may have developed an exhausted phenotype due to the tumor microenvironment.

Ex-vivo expansion of TILs utilizes freshly resected tumor tissue to extract TILs and co-culture with IL-2 to stimulate in vitro TIL expansion. Prior to reinfusion of expanded TILs, the patient receives nonmyeloablative chemotherapy regimens such as cyclophosphamide or total body irradiation, which functions to deplete inhibitory Treg cells and other lymphocytes in the patient to improve the rate of in vivo expansion of the stimulated TILs. The in-vitro-stimulated TILs, largely comprised of CD8+ and to a lesser extent CD4+ T lymphocytes, are then reintroduced into patients at high doses, together with HD IL-2, where they can recognize specific tumor antigens in a microenvironment that is now less prone to induce tolerance.

In a series of highly selected patients with advanced melanoma, 56 percent of those who received the T cell infusion had an objective response. The major limitations of this approach are that it cannot be performed in many patients (not all tumor tissues have extractable TILs and not all TILs expand *in vitro*) and that the process takes weeks from initial TIL extraction to reinfusion. Nonetheless, this approach was effective therapy for a group of patients with melanoma and has demonstrated objective responses in other malignancies (eg, cervical squamous cell carcinoma, cholangiocarcinoma).

CD3-directed therapies

Bispecific T cell engagers — Conceptually, bispecific T cell engager antibodies (BiTEs) function as linkers between T cells and specific target antigens in an MHC-subtype independent manner. They consist of a protein fragment containing two separate single-chain variable regions. One end recognizes CD3, which is expressed on all T cells, and one end recognizes the target antigen. BiTEs thus aim to induce cytotoxic T cell-mediated tumor eradication.

Because BiTEs are not MHC-specific, they can be administered to all patients regardless of human leukocyte antigen (HLA) type and do not require patient-specific processing. One consequence of this more broadly applicable approach is its relative lack of specificity in T cell recruitment when compared with the more labor-intensive method of adoptive T cell transfer. Because many different T cell subtypes express CD3, BiTEs recruit polyclonal cytotoxic T cells, Th1 and Th2 CD4+ cells, and Tregs.

The most well developed BiTE is blinatumomab, which has specificity for CD19 antigen found on many B cell malignancies and the Fc region of the CD3 receptor found on T lymphocytes. Blinatumomab was given accelerated approval by the US Food and Drug Administration (FDA) for Philadelphia-chromosome negative B-ALL.

Monoclonal TCRs — Another approach to increasing effector T cell function against a particular antigen is engineering a soluble TCR (CD8) to recognize a particular antigen target and fusing this to the variable fragment that recognizes an effector target, such as CD3. The ability to engineer a TCR rather than an antibody fragment can lead to higher affinity for a given peptide chain and allow for targeting of intracellular peptide fragments. This approach must be engineered using a specific MHC class 1 molecule, and complications have occurred through TCR cross-recognition of other antigens. MHC A*02-restricted TCRs are furthest along in clinical development because these are the most common alleles (50 percent) in people of Western European descent. See the figure for a simplified schematic representation of the key differences in the above four T cell-directed therapies.

Oncolytic viruses — Oncolytic viruses mediate antitumor effects in several ways. Viruses can be engineered to efficiently infect cancer cells preferentially over normal cells, to promote presentation of tumor-associated antigens, to activate "danger signals" that promote a less immune-tolerant tumor microenvironment, and to serve as transduction vehicles for expression of immune modulatory cytokines.

The agent furthest along in clinical development is talimogene laherparepvec (T-VEC), which utilizes an attenuated herpes simplex virus 1 virus to overexpress granulocyte macrophage colony-stimulating factor (GM-CSF), which promotes dendritic cell mediated antigen presentation. In a randomized trial comparing T-VEC with GM-CSF alone, intratumoral injections of T-VEC produced an improved durable response rate compared with intratumoral GM-CSF alone.

Numerous other virus backbones are under clinical or preclinical investigation, including adenovirus [117-120], reovirus, Newcastle disease virus, and others.

Oncolytic virus plus checkpoint inhibition — Injection of oncolytic viruses may synergize with checkpoint inhibitors by increasing CD8+ T cell infiltration and IFN gamma signaling as well as upregulating PD-L1 in the microenvironment. In a randomized trial of ipilimumab with or without T-VEC, the combination had a higher response rate than ipilimumab alone (39 versus 18 percent). A phase 1 trial of T-VEC plus pembrolizumab in patients with melanoma suggested that responses were independent of baseline immune infiltration.

Therapies directed at other cell types in tumor microenvironment — In tumor immunology, cell types other than tumor-specific and circulating T cells contribute to an effective versus a suppressed immune response, and thus represent additional targets for immunotherapy beyond T cells.

Natural killer cells — The biology of natural killer (NK) cells is complex. NK cell infiltrates in solid tumors, and metastases have been associated with an improved prognosis, although the use of CD56 or CD57 markers also expressed on T cell subsets (eg, CD8+ T cells) and some tumors may somewhat confound these findings. The killer immunoglobulin-like receptor (KIR) genes are expressed by NK cells and bind to HLA molecules on normal host cells. Cancer cells, which often lose HLA expression, are recognized by NK cells as missing their HLA molecules and are consequently destroyed by the NK cells.

Anti-KIR antibodies have shown preclinical efficacy in lymphoma, multiple myeloma, and acute myelogenous leukemia (AML). In clinical trials, a phase I study of IPH2101 was safe in patients with AML in first remission. There were no objective responses as a single agent in patients with relapsed/refractory multiple myeloma, but results were more promising when administered in conjunction with lenalidomide in this population. Lirilumab (BMS986015) is the other anti-KIR antibody undergoing early stage trials alone and in combination in hematologic malignancies and solid tumors.

Macrophages — The presence of intratumoral macrophages can portend a poor prognosis. Although an oversimplification, the general categorization of macrophages into classically activated phenotype (M1) and alternatively activated (M2) suggests that in the context of malignancy, M2 macrophages play a pro-tumoral role due to their involvement in immunosuppression, angiogenesis, and tumor cell activation.

Intratumoral macrophages are largely recruited by C-C chemokine ligand 2 (CCL2) or colony-stimulating factor 1 (CSF-1), and pre-clinical and clinical data have focused on targeting the CSF-1/CSF-1 receptor axis. The antitumor impact of CSF-1 receptor (CSF-1R) inhibition in pre-clinical models varies, but there are promising data in combination with other modalities such as chemotherapy, radiation therapy, angiogenic inhibitors, adoptive cell transfer, as well as when used in conjunction with CTLA-4 and PD-1 blockade in the challenging setting of pancreatic ductal adenocarcinoma.

Examples of CSF-1R inhibitors with clinical activity include emactuzumab (RG7155) and pexidartinib (PLX3397).

IDO — Indoleamine 2,3-dioxigenase 1 (IDO1) catalyzes the rate-limiting step in the conversion from the essential amino acid *L*-tryptophan (Trp) into *L*-kynurenine (Kyn). IDO1 expression by tumors can promote evasion of immune surveillance by suppressing T cell function and impairing immune surveillance.

Although potentially promising activity was seen in early phase trials, a randomized phase 3 study of pembrolizumab with or without epacadostat did not show benefit compared with the combination. This negative result has resulted in diminished interest in clinical development of IDO inhibitors.

Vaccines — There is a long history of attempting to harness the adaptive immune recognition of a cancer-related antigen to effect antitumor responses. Vaccine methods range widely, and a full review is outside the scope of this article.

A simplistic way to view vaccine development method is that varying types of antigens, administration schedules, and accompanying immune adjuvants can influence an adaptive immune response. Antigen choices range from simple peptides, which are easy to administer but affect a narrow antigen spectrum and are often restricted by specific HLA class 1 molecule expression that allows efficient antigen presentation, to whole cell preparations that offer a broader range of antigens but are more costly and time-consuming to prepare.

The only currently approved vaccine-based therapy for advanced cancer is sipuleucel-T, which is an autologous dendritic-cell preparation engineered to target prostatic acid phosphatase (PAP) that demonstrated an overall survival benefit in men with castrate-resistant prostate adenocarcinoma. Patient blood undergoes leukapheresis and is exposed ex vivo to PAP fused to GM-CSF. Theoretically, GM-CSF fosters maturation of dendritic cells and other APCs to present PAP to the patient's T cells, which then recognize the PAP. However, the degree of PAP-specific T cell proliferation at week 6 did not correlate with survival in the study, suggesting that additional immunologic mechanisms may explain this survival benefit.

Single-peptide vaccines continue to be tested extensively, especially in "immunogenic" cancers such as melanoma. They have largely shown disappointing efficacy in preventing recurrence or prolonging survival. As an example, in a randomized phase III trial of 185 patients, those who received the combination of IL-2 plus the HLA-A*0201- MHC-specific vaccine against the surface glycoprotein gp100 had a higher response than those who received IL-2 alone (22 versus 10 percent), and there was a nonsignificant trend toward improved survival (17 versus 11 months). However, in the randomized clinical trial that demonstrated a survival benefit for ipilimumab with or without this gp100 vaccine, the vaccine did not improve survival over ipilimumab alone.

Given the increasing understanding of the importance of immune recognition of multiple patient-specific, tumor-specific antigens, current efforts to develop therapeutic vaccines against cancer are beginning to explore the use of individualized pooled antigens. This suggests that patient-specific vaccination approaches may be feasible, particularly in immunogenic tumors such as melanoma, non-small cell lung cancer, mismatch-repair deficient colorectal carcinoma, and bladder carcinoma.

IMMUNOTHERAPY RESPONSE CRITERIA

Patterns of response — Evaluation of the effectiveness of immune checkpoint inhibitors and other forms of immunotherapy requires an understanding of the potentially different patterns of response seen with these classes of agents. The patterns of response to treatment with these immunotherapy agents can differ from those with molecularly targeted agents or cytotoxic chemotherapy in several important respects:

- Patients may have a transient worsening of disease, manifested either by progression of known lesions or the appearance of new lesions, before the disease stabilizes or tumor regresses. Therefore, some caution should be taken in abandoning therapy early. However, these delayed responses are generally not observed in patients with symptomatic deterioration, so continuing therapy beyond progression is not recommended in these patients.
- Responses can take longer to become apparent compared with cytotoxic therapy.
- Some patients who do not meet criteria for objective response can have prolonged periods of stable disease that are clinically significant.

Response criteria — Immune-related response criteria (irRC) have been proposed to properly recognize the nontraditional patterns of response occasionally seen with checkpoint inhibitors and some other immunotherapies.

- Immune-related complete response – Complete resolution of all measureable and nonmeasurable lesions, with no new lesions. A complete response must be confirmed by a second, consecutive assessment at least four weeks later.
- Immune-related partial response – A decrease in the total tumor burden of 50 percent or more compared with baseline, which must be confirmed by a second, consecutive assessment at least four weeks later. This category allows for the inclusion of progression of some lesions or the appearance of new lesions as long as the total tumor burden meets the response criterion.
- Immune-related stable disease – Not meeting the criteria for either a partial or complete response or for progressive disease.
- Immune-related progressive disease – An increase in tumor burden of 25 percent or more relative to the minimum recorded tumor burden. This must be confirmed by a second, consecutive assessment no fewer than four weeks after the initial documentation of an increase in tumor.

Use of these immune-related response criteria is important because the application of traditional Response Evaluation Criteria In Solid Tumors (RECIST) criteria in patients treated with checkpoint inhibitors may lead to premature discontinuation of treatment in a patient who will eventually respond to treatment or have prolonged disease.

Consensus-based criteria for response to immunotherapy (iRECIST) have been developed for use in trials testing immunotherapy. They may also be applicable to patients receiving immunotherapy in a non-trial setting.

These criteria are based upon RECIST 1.1, with some modifications, and are prefixed with an "i" (immune). These iRECIST criteria build upon the previously described response criteria (irRC), which were also based upon RECIST and World Health Organization (WHO) guidelines for response assessment in patients treated with chemotherapy. The major modifications are:

- The definitions of measurable and nonmeasurable disease; numbers and sites of target disease are the same as for RECIST 1.1.
- The biggest difference from RECIST 1.1 (and similar to the irRC) is that the development of new lesions during therapy is classified as immune unconfirmed progressive disease (iUPD); immune confirmed progressive disease (iCPD) is only assigned if at the next assessment, additional new lesions appear or there is an increase in the size of the new lesions (≥5 mm for the sum of the new lesion targets or any increase in a new lesion nontarget); the appearance of new lesions when none have previously been recorded can also confirm iCPD.
- The response assignment categories are immune complete response (iCR), immune partial response (iPR), iUPD, iCPD, and immune stable disease (iSD).
- Time point responses are defined according to whether or not there was a prior iUPD in any category.

Immune-modified Response Evaluation Criteria In Solid Tumors (imRECIST) have also been developed to utilize a unidimensional measurement system based upon the RECIST 1.1 system. The imRECIST may offer advantages compared with RECIST by recognizing the potential benefits from treatment in patients who have a transient progression after initiation of immunotherapy.

In clinical practice, patients receiving any immune-based therapy and whose tumors show initial growth should be assessed carefully for signs and symptoms of clinical benefit or progression; the majority of patients will have true progressive disease. In the absence of symptomatic progression, however, a short-term repeat scan is reasonable prior to considering immune-based therapy a failure.

PREDICTORS OF RESPONSE TO IMMUNE-BASED THERAPY

As immune checkpoint blockade and other immune-based therapy approaches lead to broad treatment advances among patients with advanced cancer, an important consideration is how to best select patients whose tumors will respond to these therapies.

The candidate biomarker that has been studied most extensively is programmed death ligand 1 (PD-L1) expression in trials utilizing programmed cell death-1 (PD-1) blockade. PD-L1 and PD-1 expression are dynamic markers that change in relation to local cytokines and other factors, and the thresholds that separate "positive" and "negative" PD-L1 expression remain under debate.

Still, most trials with either retrospective or prospective assessments of PD-L1 status have shown trends for increased response rates to PD-1 blockade in PD-L1 "positive" tumors. Most notably, in patients with newly diagnosed advanced non-small cell lung cancers (NSCLCs) with ≥50 percent PD-L1 expression who were randomized to pembrolizumab or chemotherapy, those randomized to pembrolizumab had a significantly improved objective response rate, progression-free survival, and overall survival. On the basis of this trial, PD-L1 expression is now a routine diagnostic marker for patients with newly diagnosed NSCLC. The potential applicability of PD-L1 in other disease settings is still uncertain.

It is important that no patient with an advanced cancer and an established clinical rationale for use of an immune therapy agent should be refused immune therapy on the basis of lack of PD-L1 expression or any other investigational biomarker.

Beyond PD-L1 expression, another predictive biomarker that is being explored is somatic mutation burden. Preliminary data suggest that tumors with high rates of somatic mutations (ie, sun-exposed cutaneous melanoma, NSCLC, bladder cancer, and microsatellite-unstable colorectal carcinomas) have a higher chance of benefiting from immune checkpoint blockade than tumors with lower rates of somatic mutations.

Additional gene-expression-based signatures for immune response are also under active investigation.

SUMMARY

The pace of discovery in the fields of immunology and cancer biology is accelerating due to the foundation laid decades ago. As our understanding of the role of the immune system in tumor initiation, progression, and metastasis evolves, continued progress is likely in the treatment of malignancy.

Checkpoint inhibition has already become a primary treatment modality for patients with a broad diversity of cancers, resulting in significantly prolonged survival in some patients. Trials exploring other malignancies and a wide variety of immunotherapy combinations are in progress and should extend these results.

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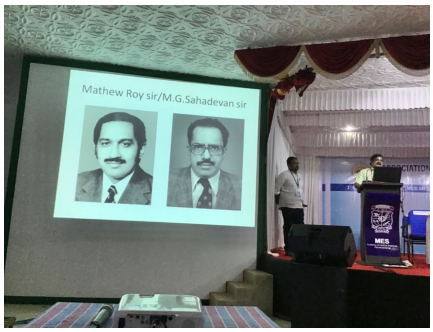

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