Post-Resection Surveillance in GI Cancers

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Abstract Recurrence after curative resection of gastrointestinal (GI) cancers is common. Early detection of resectable recurrences may result in a curative resection. In unresectable recurrences, early detection may improve the quality of life by palliation or with the use of newer chemotherapeutic drugs. The guidelines regarding follow-up of patients after curative resection of GI cancers are from the West which is very different from the Indian population in terms of a disease pattern and social milieu. The guidelines which are commonly used are also not strictly followed. We have proposed in this article the protocols which we follow at our centre after curative resection of GI cancer and how these are different from the guidelines proposed by the West.

Keywords Recurrence · Surveillance · Guidelines · GI cancers

Introduction

Surgical resection remains the primary treatment modality for most gastrointestinal (GI) cancers with non-metastatic disease. However, post-resection surveillance is important because recurrence rates after surgery are high even if adjuvant radiotherapy and/or chemotherapy are used.

Early diagnosis of recurrence in patients with GI cancers renders them more suitable for further treatment including curative resection. The benefit is greater if these recurrences are asymptomatic. This is especially true for patients with colorectal cancer because repeated extirpation is associated with a good prognosis, and highly effective chemotherapy is also now available. Although there are standard guidelines for post-resection surveillance, these are rarely followed strictly.

The guidelines that have been proposed previously were from western countries where the disease pattern and social milieu are different with the resources also being more plentiful and so may not be applicable to our Indian patient population. For example, the incidence of colorectal polyps is low in India, and therefore repeated proctosigmoidoscopy may not be required for our patients after curative resection of colorectal cancers. In this article, we propose a strategy that might be followed for patients with GI cancers in India after they have undergone surgical resection of their tumour.

Recurrence Patterns

The majority of recurrences develop within the first 2 years after operation. These recurrences can be local (at the tumour bed and anastomotic site) or distant. The most common recurrence sites for the various GI cancers are as follows:

1. *Loco-regional* recurrences are more common in colorectal, stomach, liver and gall bladder cancers.
2. *Distant* recurrences are more common in oesophageal cancers.
3. *Both local and distant* recurrences frequently occur in pancreatic cancers.

We will discuss GI cancers under two broad headings:

- A. Luminal (colorectal, stomach, oesophagus) and

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B. Hepatopancreato-biliary (liver, pancreas, gall bladder, bile duct) cancers.

Luminal Cancers

Colorectal Cancer

The incidence of colorectal cancer (CRC) in India is low as compared to the West but is expected to rise in the near future [1] with the change in our eating habits and lifestyles becoming more ‘westernized.’ Surgery remains the treatment of choice for patients who present with non-metastatic disease. However, even after curative surgery, 5-year survival rates are 70 % or lower, and most patients require adjuvant chemotherapy and/or radiotherapy for stage II/III disease [2]. Intensive post-operative surveillance is now recommended for these patients [3–5].

Rationale for Surveillance Patients with recurrence after potentially curative resection may experience high cure rates if the recurrence is localised, and surgery is also curative if the metastatic disease is limited particularly to the liver and lung [6–10]. In fact, 5-year survival rates of 30–63 % have been reported after resection of lung metastases [6–8]. A 5-year survival of more than 40 % and a median survival of more than 30 months have been achieved in selected patients after partial liver resection for colorectal metastases [11].

Asymptomatic recurrences identified by post-operative surveillance are more likely to be suitable for curative resection and have high overall survival rates after surgery [10, 12, 13]. In a meta-analysis of 3,283 patients, comparing intensive follow-up with minimal or no follow-up, patients with intensive follow-up had 9 % better survival rates. Asymptomatic recurrences were detected more frequently in patients who underwent intensive surveillance (45 vs 8 %), and these were more likely to be resectable (35 vs 21 %) [13]. However, these data should not preclude surgeons from operating upon symptomatic recurrences which may also be resectable [14] (Fig. 1).

Is Surveillance Required for Stage I Disease? Post-resection surveillance strategies generally focus on patients with stage II and III disease. Aggressive surveillance protocols are not recommended for stage I disease because index surgery alone was probably curative. However, in the Clinical Outcomes of Surgical Therapy (COST) trial which included patients with stage I ($n=265$), IIA, IIB, and III disease, secondary analysis revealed that salvage rates with post-operative surveillance of early-stage disease were similar to late-stage disease [15]. The authors in this study concluded

that a similar surveillance strategy should be adopted for stage I disease as well.

Which is Better—Intensive/Less Intensive Surveillance Strategy?

Most randomised trials have failed to show a survival benefit with intensive post-operative surveillance strategy [16–19], although a few have shown results favouring intensive surveillance [20]. Unfortunately, they had some major drawbacks which include (1) the few patients in some reports, (2) their non-optimal design and (3) the inclusion of patients with stage I disease. However, meta-analyses of these randomised trials have shown a significant survival benefit with intensive surveillance compared to non-intensive surveillance [3–5, 21]. A meta-analysis also showed that intensive post-operative surveillance was cost-effective [22].

Tests Available Surveillance strategy should include tests which can identify tumour recurrences early. The common site of this after colorectal cancer resection is the liver except for distal rectal cancers in which lung metastases are more common. The surveillance methods should include the following:

1. History and physical examination: Recurrent disease can be identified in only a few patients based on clinical examination alone [10]. In a study of patients with stage II/III colon cancer, routine physical examination failed to identify any resectable recurrence [14]. However, there are clear benefits of a history and physical examination in that it maintains a good doctor–patient relationship and helps in discussing the results of tests and the importance of routine surveillance.
2. Carcino-embryogenic antigen (CEA): The serum CEA is the only laboratory test recommended for surveillance after resection in colorectal cancer and its measurement the most cost-effective test for detecting recurrences [14, 23]. Estimation of CEA in patients with established disease correlates with the disease burden and has a prognostic value. If the CEA levels are high after curative resection, the risk of residual disease is also high with a 70 % sensitivity of detecting disease relapse [24]. However, it must be remembered that approximately 30–40 % of CRC recurrences do not produce CEA. *Why CEA levels should be aggressively monitored?* Resection of limited metastases in follow-up after colorectal cancer operations results in long-term disease-free survival in up to 40 %. Studies have shown that CEA levels are elevated earlier compared with other detection methods in those patients with recurrent disease [25].

Fig. 1 A 33-year-old female underwent left hemicolectomy in April 2011 for carcinoma of the left colon and presented within 6 months with PET-CT showing fluorodeoxyglucose (FDG) avid lymph node mass at the bifurcation of left common iliac vessels, encasing the left ureter and mesentery on the left side of the pelvis (**a**). Colonoscopy revealed an ulcer 30 cm from the anal verge. After receiving adjuvant chemotherapy, she underwent R0 resection involving anterior resection, segmental ileal resection, ileo-rectal anastomosis, resection of lymph node mass, left oophorectomy and left nephrectomy because of infiltration of tumour to the left ovary, distal ileum and left ureter. She again presented

in March 2012 with a CT showing interaortocaval, left external iliac artery and right internal iliac lymph node mass (**b**). She underwent resection of left psoas mass, right ovary, left common iliac artery, interaortocaval and right common iliac artery lymph nodal mass and aorto-iliac reconstruction using PTFE graft. One month later, her PET-CT showed FDG avid nodular mass in the left psoas muscle (**c**) for which local resection was done. She is well on follow-up and shows the benefits of aggressive surveillance and treatment strategies for carcinoma of the colon

3. Complete blood counts (CBC), liver function tests, chest X-ray and faecal occult blood testing: There is no evidence to suggest that routine testing improves detection rates.
4. Computed tomography (CT) scan: The value of routine post-operative CT scans of the abdomen, pelvis and chest has been supported by meta-analysis. In one meta-analysis, survival benefit was found to be maximal if both CEA levels and CT scans were incorporated into the surveillance strategy [4]. In the USA intergroup studies for colon cancer, a CT scan was not included in a routine post-operative surveillance strategy in contrast to two European trials which included CT scans. In the European trials, 40 % of patients underwent potentially curative resections, while in US studies, the figure was only 20 % [10, 14, 26, 27].
5. Positron emission tomography (PET) scan: Routine PET scanning to detect recurrence is not recommended. PET scanning may reveal early recurrences and some second primary tumours. The main disadvantage, however, is the number of significant false positive and false negative results. However, PET scanning does have a role in a patient with elevated CEA levels and other imaging studies being negative.
6. Colonoscopy: If preoperative colonoscopy could not be performed in a patient (for example with an obstructed

Fig. 2 Management in a patient with elevated serum carcino-embryonic antigen (CEA) after curative resection of colorectal cancer

colonic cancer), it should be performed within 6 months post-operatively to diagnose synchronous lesions. Post-operative endoscopic surveillance may detect anastomotic recurrences and metachronous lesions; most of which develop within the first 2–3 years after surgery. Colonoscopy surveillance is required only for 5 years after primary resection, unless some abnormality is detected during standard surveillance [28].

7. Proctosigmoidoscopy: This has a role in patients with rectal cancer since they have a higher likelihood of anastomotic recurrence. It is also less expensive and safer than a full colonoscopy.

Treatment of Recurrence The treatment of recurrence is summarised in the flow chart (Figs. 2 and 3).

Rationale for Modifications in National Comprehensive Cancer Network Guidelines [29] The National Comprehensive Cancer Network (NCCN) guidelines have been suggested according to the western population which may not be applicable to our Indian population. We therefore have modified the NCCN guidelines and proposed the guidelines as suited to our patient population while keeping in mind not to miss any resectable recurrences (Table 1). We follow these guidelines at our centre during follow-up period after operation. The main reasons for such modifications are the

Fig. 3 Management of a patient with documented metastases after curative resection of colorectal cancer

increased cost of vigorous testing, as more than three fourths of our population pay from their own pockets and have no health insurance, and the long distances the people may need to travel to consult their surgeon. In Indian population, the incidence of colonic and rectal polyps is also low as compared to the west, and therefore, routine proctosigmoidoscopy is not recommended.

Stomach Cancer

The most common sites of recurrence are local (anastomotic site/gastric remnant) or in the liver and peritoneum. Aggressive surveillance strategies are usually expensive and unnecessary since these patients have a poor prognosis after relapse. Most of these patients are not candidates for liver resection and even after resection the prognosis remains poor. Lee and colleagues in a study of post-operative surveillance with endoscopy involving 834 patients with early and advanced gastric cancers concluded that routine endoscopy did not improve survival rates [30]. Similar studies involving post-operative surveillance strategies with endoscopy and PET scans have failed to show a survival benefit [31, 32].

We at our centre follow the guidelines written below with only slight modifications to the NCCN guidelines since the treatment of recurrences does not yield major benefits in this group of patients (Table 2).

Nutritional Counselling The diet should be rich in protein, low in carbohydrate and low in concentrated sweets. It should

be rich in iron and vitamin B₁₂, and oral iron and calcium supplements should be given. Vitamin B₁₂ injections should be administered monthly when indicated. The patient should

consume five to six small meals a day instead of two large ones because of the absence of the stomach.

Treatment of Recurrence

care	1. Karnofsky performance score $\geq 60\%$
or ECOG performance score ≤ 2	}	Chemotherapy/ clinical trial/ supportive
	2. Karnofsky performance score $< 60\%$
or ECOG performance score ≥ 3	}	Best supportive care

Oesophageal Cancer

Most of the recurrences after resection develop within 1 year, and 60 % of these are at distant sites. However, no trials have been done for post-operative surveillance of oesophageal cancer so there are no data to suggest that detection of asymptomatic

recurrences improves longevity or quality of life. The modifications suggested to the NCCN guidelines are given in Table 3.

Upper GI Endoscopy It should be done only if indicated clinically. During the procedure, mucosal surface changes should be assessed, and biopsies if required should be taken

Table 1 Guidelines proposed and practised at our centre for colorectal cancer surveillance after a curative resection as compared to NCCN guidelines

	NCCN guidelines	Proposed guidelines
History and physical examination	Every 3–6 months for the first 2 years, every 6 months during 3–5 years and annually thereafter	Every 3–6 months for the first year, every 6 months thereafter for 5 years and annually thereafter
Serum CEA	Every 3–6 months for 2 years and then every 6 months for a total of 5 years	Every 3–6 months for the first year, every 6 months for 5 years and thereafter if clinically indicated
USG abdomen	Not recommended	Every 3–6 months for 1 year; every 6 months thereafter if CT scan was not done
CT scan	Annual CT of the chest, abdomen and pelvis for 3–5 years	Annual CT of the chest, abdomen and pelvis for 3 years and then as clinically indicated
Colonoscopy	At 1 year, then at 3 years and then every 5 years thereafter; if abnormal, repeat in 1 year	At 1 year, then at 3 years and then every 5 years thereafter; if abnormal, repeat in 1 year
Proctosigmoidoscopy	At 6-month intervals for 5 years	Not recommended since it is not routinely available as an office procedure and is unlikely to yield curable recurrences missed by colonoscopy

Table 2 Guidelines proposed and practised at our centre for stomach cancer surveillance after a curative resection as compared to NCCN guidelines

	NCCN guidelines [29]	Proposed guidelines
History and physical examination	Every 3–6 months for 2 years, every 6–12 months for 3–5 years and then annually	Every 3–6 months for 1 year and annually thereafter
Complete blood counts and other blood chemistry	As clinically indicated	Every 3–6 months for 1 year and annually thereafter and as clinically indicated
Radiologic imaging	As clinically indicated	As clinically indicated
Endoscopy	As clinically indicated	Only if clinically indicated
Nutritional counselling	Monitor for nutritional deficiency and treat as indicated	Same as NCCN

(at least four to six biopsies) from the abnormal mucosal areas and strictures. Endoscopic dilation should be done if anastomotic stenosis is detected. Endoscopic ultrasound (EUS) if performed in conjunction with endoscopy has a high sensitivity. EUS also has therapeutic benefit as it can be used for guided fine-needle aspiration if suspicious lymph nodes or areas of wall thickening are seen.

Nutritional Counselling It includes detecting nutritional deficiencies and treat them accordingly. The patient should consume soft diet and chew food properly before swallowing and should stay upright for 1–3 h after eating. Liquids should be avoided at meals. He or she should consume frequent small meals instead of two large meals. Treatment of recurrence is shown in Fig. 4.

Hepatopancreato-Biliary Cancers

Hepatocellular Cancer

Hepatocellular cancer is an aggressive tumour. Underlying cirrhosis is present in >90 % of patients, and most of these

are chronic hepatitis B and/or hepatitis C virus positive. The majority of recurrences after resection are intrahepatic (>80 %) and occur within 2 years [33]. Post-operative surveillance is required because of the following:

1. High risk of developing recurrence and progression to liver failure after resection
2. Underlying chronic liver disease provides a field for the development of second primary tumours
3. Underlying chronic liver disease requires regular monitoring and assessment of hepatic reserve.

We follow the same guidelines as laid by the NCCN [29]:

- Imaging: Every 3–6 months for 2 years and then every 6–12 months.
- AFP levels: If initially elevated, every 3–6 months for 2 years and then every 6–12 months.

Treatment If intrahepatic recurrence, the treatment options include repeat hepatectomy, radiofrequency ablation, trans-arterial chemo-embolisation and liver transplantation (Fig. 5), and if extrahepatic recurrence, systemic therapy.

Table 3 Guidelines proposed and practised at our centre for oesophageal cancer surveillance after a curative resection as compared to NCCN guidelines

	NCCN guidelines [29]	Proposed guidelines
History and physical examination	Every 3–6 months for 2 years, every 6–12 months for 3–5 years and then annually	Every 3–6 months for 1 year and then annually
CBC and other chemistry profile	As clinically indicated	Every 3–6 months for 1 year and then annually
Radiologic imaging	As clinically indicated	As clinically indicated
Upper GI endoscopy	As clinically indicated	Only if clinically indicated
Nutritional counselling	Monitor for nutritional deficiencies and modify eating habits	Monitor for nutritional deficiencies and modify eating habits

Fig. 4 Treatment of recurrence after curative oesophageal cancer resection

Fig. 5 Recurrent hepatocellular cancer in the liver after a previous resection (**a**) and salvage liver transplant using the right lobe from a living donor done in the same patient (**b**)

Mass on imaging/jaundice

1. History & Physical examination
2. CT/MRI
3. LFTs
4. Consider CEA, CA 19-9
5. Consider staging laparotomy

Resectable

Unresectable

Enbloc hepatic resection

1. Chemotherapy
(Gemcitabine/ cisplatin combination)
2. Clinical trial
3. Supportive care
4. Biliary drainage if jaundice.

Fig. 6 Treatment of recurrence after a curative resection of gall bladder cancer

Gall Bladder Cancer

Recurrence after gall bladder resection is mainly loco-regional. Port site recurrences have been documented in patients undergoing laparoscopic cholecystectomy in incidentally found gall bladder cancer. We follow the same guidelines as laid by the NCCN [29]:

- Imaging every 6 months for 2 years
- No data to support aggressive surveillance.

Treatment of recurrence is shown in Fig. 6.

Cholangiocarcinoma

The guidelines followed after resection, and the treatment of recurrence is the same as gall bladder cancer.

Pancreatic Cancer

The most common sites of recurrence of pancreatic adenocarcinoma after curative resection are local (60–80 %) and hepatic (50–65 %) with the majority occurring within 2 years.

Table 4 Guidelines proposed and practised at our centre for pancreatic cancer surveillance after a curative resection as compared to NCCN guidelines

	NCCN guidelines	Proposed guidelines
History and physical examination	Every 3–6 months for 2 years and then annually	Every 3–6 months for 2 years and then annually
CA 19-9 levels	Every 3–6 months for 2 years	Every 6 months for 2 years only if raised preoperatively
Ultrasound abdomen	Not recommended	Every 6 months for 2 years and then if indicated clinically
CT scan	Every 3–6 months for 2 years	Only if indicated clinically

Our centres' protocol after Whipple's pancreatoduodenectomy procedure during follow-up is shown in Table 4. Treatment of recurrence is shown in Fig. 7.

For other cancers like intrapapillary mucinous neoplasms (IPMNs), gastrointestinal stromal tumours, carcinoids and other neuroendocrine tumours, we follow the international consensus guidelines.

Intrapapillary Mucinous Neoplasms

Risk of recurrence after resection for non-invasive IPMNs is 7 %, and for invasive IPMNs, 25–30 %.

Surveillance Guidelines The following are the international consensus guidelines for surveillance:

- Lesions of <10 mm=CT/magnetic resonance cholangiopancreatography (MRCP) every 12 months
- Lesions 10–20 mm=CT/MRCP every 6–12 months
- Lesions of >20 mm=CT/MRCP every 3–6 months

If no changes in the cyst after 2 years, interval of follow-up is lengthened (2–3 years).

These patients are at a high risk of developing extrapancreatic malignancies: colon cancer, gastric cancer, breast cancer and prostate cancer. Therefore, regular follow-up is also required in

the form of upper gastrointestinal endoscopy, colonoscopy, prostate-specific antigen and mammography.

Gastrointestinal Stromal Tumours

- History and physical examination every 3–6 months
- Abdominopelvic CT every 3–6 months.

Pancreatic Neuroendocrine Tumours

- a. Three to 12 months post-resection:
 - History and physical examination
 - Appropriate tumour markers
 - Multiphasic CT/MRI
- b. More than 1 year post-resection, every 6–12 months
 - History and physical examination
 - Consider appropriate tumour markers
 - Multiphasic CT/MRI as clinically indicated

Carcinoids

No surveillance is required for appendiceal carcinoids of <2 cm and rectal carcinoids of <1 cm. Surveillance is recommended for other carcinoids:

Fig. 7 Treatment of recurrence detected on imaging studies in a patient who underwent curative resection for pancreatic cancer

- a. Three to 12 months post-resection:
 - History and physical examination
 - Urine 5-HIAA
 - Consider abdominal or pelvic CT/MRI
 - Consider assay for serum chromogranin A levels.
- b. More than 1 year post-resection:
 - History and physical examination
 - Consider urine 5-HIAA
 - Abdominal or pelvic CT/MRI as clinically indicated
 - Consider assay for serum chromogranin A levels.
- c. For rectal carcinoids 1–2 cm:
 - Proctoscopy at 6–12 months in addition to the above tests.
- d. For gastric carcinoids with increased gastrin levels:
 - Oesophagogastroduodenoscopy every 6–12 months for the first 3 years.

In *summary*, definitive surveillance protocols for various GI cancers have been recommended, but they should be modified in different regions according to their patient populations and the diagnostic modalities available. Non-compliance with these protocols is the main reason behind missing resectable recurrences. Early detection of intrahepatic recurrence of HCC may increase the survival rates by resection/salvage transplantation. Cancers of the oesophagus, stomach, pancreas and gall bladder do not have effective adjuvant chemotherapy and are usually much more advanced at the time of recurrence. Whether routine surveillance in these cancers improves detection rates at the time of recurrence is controversial, but it does result in an improvement in the quality of life by providing better palliative care. With newer and more effective chemotherapeutic drugs and better diagnostic modalities available, patients may also benefit from strict protocols in these GI cancers in the future. The yield of such rigorous protocols is much more for colorectal cancer recurrences as compared to other GI cancers. These protocols should be incorporated in the discharge summaries of the patient so that these can be followed strictly.

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