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Review Article

Gastrointestinal cancers in India: Treatment perspective

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Abstract

GI cancer is not one cancer but is a term for the group of cancers that affect the digestive system including gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), esophageal cancer (EC), and pancreatic cancer (PC). Overall, the GI cancers are responsible for more cancers and more deaths from cancer than any other organ. 5 year survival of these cancers remains low compared to western world. Unlike the rest of the world where organ based specialities hepatobiliary, pancreatic, colorectal and esophagogastric exist , these cancers are managed in India by either a gastrointestinal surgeons, surgical oncologist, or a general surgeon with varying outcomes.The aim of this review was to collate data on GI cancers in indian continent. In colorectal cancers, data from tertiary care centres identifies the unique problem of mucinous and signet colorectal cancer. Results of rectal cancer resection in terms of technique (intersphincteric resection, extralevator aper, minimal invasive approach) to be comparable with world literature. However long term outcome and data regarding colon cancers and nationally is needed. Gastric cancer at presentation are advanced and in surgically resected patients, there is need for a trial to compare chemoradiation vs chemotherapy alone to prevent loco regional recurrence. Data on minimal invasive gastric cancer surgery may be sparse for the same reason.Theree is a lot of data on surgical techniques and perioperatve outcomes in pancreatic cancer.There is a high volume of locally advanced gallbladder cancers with efforts on to decide whether neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy is better for down staging. Considering GI cancers, a heterogeneous disease with site specific treatment options and variable outcomes, the overall data and outcomes are extremely variable.Young patients with pathology unique to the Indian subcontinent (for example, signet ring rectal cancer, GBCs) need focussed attention. Solution for such pathology needs to come from the Indian continent itself. Joint efforts to improve outcomes for GI cancer can be integrated under the national cancer grid program.

Key words: Colorectal cancers, gallbladder cancers, gastric cancers, India, pancreatic cancers

Introduction

Gastrointestinal cancer

Cancer is known as one of the major causes leading to many disorders, death, and disabilities worldwide. Among all organ cancers, gastrointestinal tract cancers (GI cancers) present an interesting pattern in distribution over the world.[1] GI cancer is not one cancer but is a term for the group of cancers that affect the digestive system including gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), esophageal cancer (EC), and pancreatic cancer (PC). Overall, the GI cancers are responsible for more cancers and more deaths from cancer than any other cancers. There is an increasing burden (incidence and mortality) in GI cancer worldwide, and Asia is no exception.

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There are very limited data available in the field of GI cancers in India. Most of the studies are available as retrospective analysis, and very few prospective, randomized studies are available. This exercise is performed to collate data on GI cancers in Indian scenario.

Materials and Methods

Thorough PubMed search was made on GI cancers in India, which included individual sites also. Relevant data are collected and presented here. Studies in the form of case reports and small case studies were excluded from this analysis.

Colorectal cancer

The studies on CRC are mostly in the form of single center retrospective experiences and Phase II studies. Some studies though small yet relevant in Indian patients were included in this analysis.

Surgery in colorectal cancer

Sphincter preservation in rectal cancer

Sphincter preservation rates in low rectal cancer almost serve as an index of surgical quality. With double-stapling technique, intersphincteric resection, transanal total mesorectal excision (TME), and various techniques for transanal excision, the rates of sphincter preservation have increased in recent years.

Pai *et al*. reported from Tata Memorial Centre, Mumbai, on a consecutive series of 33 patients undergoing intersphincteric resection for low rectal cancer,[2] 70% of these patients received open surgery while the remaining were offered a laparoscopic approach. The authors reported acceptable results in terms of median blood loss (300 ml), median hospital stay (7 days), and complications rates. All distal margins were free in this series and cut resected margin positivity was 6%. Although this is a small series from a tertiary cancer institute in India, it demonstrates the feasibility of intersphincteric resection in terms of oncological adequacy and perioperative morbidity. Data on long-term functional and oncological outcomes are necessary.

Shrikhande *et al*. reported on a series of 68 patients undergoing ultralow anterior resection.[3] The mean distance of the tumor and anastomosis from the anal verge was 5.1 cm and 2.8 cm, respectively. The authors compared perioperative outcomes among 45 patients receiving neoadjuvant chemoradiation and 23 patients with upfront surgery. Both groups were comparable in terms of median blood loss and complication rates. The authors suggested that as 23 patients in the group receiving neoadjuvant therapy, who were initially planned for abdominoperineal resection (APR), ultimately received a margin-negative ultra-low anterior resection, neoadjuvant therapy might serve to increase sphincter preservation rates. However, the notion of neoadjuvant therapy increasing sphincter preservation rates has not been supported by meta-analyses and systematic reviews.[4,5]

Surgery for low rectal cancer has evolved over the last decades with extralevator abdominoperineal (ELAP) resection becoming popular for low involvement of circumferential resection margin and intraoperative perforation rates. Pai *et al*. compared ELAP to standard APR and concluded that ELAP should be the preferred approach for low rectal tumors with involvement of levators. For those cases in which levators are not involved, as shown in preoperative magnetic resonance imaging, the current evidence is insufficient to recommend ELAP over conventional APR.[6]

Surgical pathology: Nodal dissection and frozen section

Adenocarcinoma of the rectum has been classified by the World Health Organization (WHO) into various histologic subtypes. Vallam *et al*. analyzed the effect of the histologic subtype (classic, signet ring cell, and mucinous) on the clinical outcomes of patients with rectal cancer.[7] Over 3 years, 273 patients with CRC underwent curative resection. Both mucin-secreting variants were more common in younger patients and presented at a more advanced stage. Furthermore, 54% and 48% of those with signet ring cell carcinoma (SRCC) and mucinous adenocarcinoma (MAC) had node-positive disease compared with the rate in the classic variant (30%). Circumferential resection margin positivity was 24% with MAC and 19% with SRCC compared with 4% with the classic variant. Disease-free survival (DFS) for those with the classic and mucinous variants was 38.5 and 37.4 months, respectively. In contrast, it was 28.6 months in the SRCC group. The overall survival (OS) did not differ significantly. The authors concluded that rectal adenocarcinoma presents as a spectrum of disease, with progressively worsening outcomes from classic to MAC to SRCC. These aggressive variants might warrant more aggressive resection. These data from the Indian subcontinent differ from the published data from the Western countries.

The extent of nodal dissection and the nodal yield are important pathological parameters in CRC. A minimum of 12 nodes are essential for accurate pathological staging. Achieving this benchmark is not only dependent on the quality of surgical resection but also equally an outcome of meticulous pathological dissection of the resected specimen. Deodhar *et al*. reported on a study of 170 colorectal resections aimed at determining whether achieving the benchmark of 12 nodes is possible.[8] The total lymph node positivity (metastatic disease) in this study was 44.7% and the overall mean lymph node yield was 12.68 (range 0–63; median 11). Age >39 years, rectal cancer vis-a-vis colon cancer, and neoadjuvant chemoradiation were found to be associated with significantly lower lymph node yields.

Although TME in rectal cancer eliminates all mesorectal nodes, 15–25% of patients have lateral pelvic lymph node involvement, especially with rectal tumors lying below the peritoneal reflection.[9] Sinukumar *et al*. reported on the initial experience of lateral pelvic node dissection in locally advanced rectal cancer.[10] Of the 144 patients operated upon for locally advanced rectal cancer in this study, 5% had persistent lateral pelvic nodes on imaging following neoadjuvant chemoradiation. All these eight patients underwent lateral pelvic node dissection in addition to TME. Two of these eight patients (25%) had residual viable disease in these nodes. Postoperative morbidity was acceptable. Although small, this initial experience from a tertiary cancer center in India suggests a possible role of lateral pelvic node dissection in a selected group of patients with residual lateral pelvic nodes followed by neoadjuvant therapy.

A positive margin is an undisputed predictor for local recurrence following rectal surgery. This assumes particular importance in sphincter preservation where nonavailability of a negative distal margin is an absolute indication for APR. Gomes *et al*. reported on the efficacy of frozen section in evaluating the distal resection margin in anterior resection.[11] In this study, intraoperative frozen section had a sensitivity of 85.17%, a specificity of 100%, and a negative predictive

value of 99.16%. The authors concluded that frozen section is recommended in all cases of low rectal cancer, should be considered in locally advanced, poorly differentiated mid-rectal tumors, and could be avoided in upper rectal cancers.

Complete response following neoadjuvant therapy: Surgery or observation

About 15–27% of patients will experience a complete pathological response following neoadjuvant chemoradiation for rectal cancer.[12] The concept of observation alone following complete clinicoradiological response has been championed by the group from Brazil led by Habr-Gama *et al*. Reports from this group suggested that a small but definite group of patients might avoid surgery following neoadjuvant therapy with satisfactory results.[13]

Sinukumar *et al*. reported on survival rates of 64 patients with complete response (CR).[14] After a median follow-up of 30.5 months (range 11–59 months), the 3-year OS was 94.6% and the 3-year DFS was 88.5%. The locoregional and systemic recurrence rates were 4.7% and 3.1%, respectively. The authors concluded that although there are some data to suggest that CRC in India might have a younger median age of incidence and more aggressive biology in these young patients,[15] outcome in complete responders is still acceptable.

Another small study reported by Ayloor Seshadri *et al*. showed a 30% incidence of isolated local recurrence in patients undergoing observation alone following complete clinical response after neoadjuvant therapy.[16] The authors also revealed comparable rates of DFS between a comparable group of patients with complete clinical response who underwent resectional surgery. This suggests the promising role of observation alone in a selected group of patients with complete clinical response. Another single center study by Vallam *et al*. cast uncertainty about observation alone in complete responders after chemoradiotherapy (CTRT). Due to high nodal burden in mesorectum.[17] These 524 patients with predominantly low rectal tumors were treated with CTRT. Nodal positivity in even yPto tumours was 14.7%. Even in patients satisfying low-risk criteria (pathological CR [pCR], non-SRCC histology, and age >40 years), 69 patients, the residual-positive nodal disease burden is 10%. Whether this high incidence of residual nodal disease translates into a similar risk of locoregional recurrence if an organ preservation strategy is adopted is unclear. Hence, the role of observation after clinical CR to CTRT alone must be restricted to patients in clinical trials or study alone.

Minimally invasive surgery

The role of minimally invasive surgery in CRC is now supported by a number of randomized controlled trials (COST, COLOR, MRC CLASICC, and COREAN). Indian data on laparoscopic surgery for CRC are restricted to retrospective analyses of comparable groups. Results of these studies are in keeping with the results of randomized trials and show oncological equivalence in terms of margin positivity and lymph node yield. In addition, the short-term advantages of less blood loss and shorter hospital stay associated with laparoscopy are also demonstrated in these reports.[18-20] Although laparoscopy in CRC is associated with a shorter hospital stay, the surgical approach, namely, laparoscopic or open surgery, does not influence the timing of beginning adjuvant chemotherapy. Sinukumar *et al*. in a study of 181 patients, 57 of whom underwent a laparoscopic resection, showed that postoperative complications alone were responsible for delays in adjuvant chemotherapy.[21]

On analyzing 325 consecutive laparoscopic colorectal resections, Prakash *et al*. concluded that with increasing experience, laparoscopic colorectal surgery could be practiced safely with minimal conversion rates and morbidity. Increasing experience also enables one to select advanced cases for laparoscopy with better short-term outcomes.[22]

Complete mesocolic excision

Complete mesocolic excision (CME) for colon cancer has been recently shown to be associated with a superior DFS in a large Danish population-based study.[23] The only Indian data on CME to date have been reported by Subbiah *et al*. The authors reported on a series of 212 patients with right colon cancer who underwent laparoscopic CME, with an initial retrocolic endoscopic tunnel approach. Conversion rate was 2.8%, and mean operative time was 142 ± 28.4 min with median hospital stay of 5 days (range 4–11). The median count of lymph node harvested was 24 (range 10–42) and CME was achieved in 93.8% patients. With an overall morbidity rate of 9.9%, the authors concluded that laparoscopic CME is a safe and feasible technique.

Radiation with or without chemotherapy in rectal cancer

Audit of outcomes of patients treated with standard preoperative chemoradiation

A retrospective series of 182 patients of rectal cancer who received neoadjuvant radiation therapy (NART) was published from Tata Memorial Centre. Of the 182 patients who received long-course NART with concurrent capecitabine, 131 (72%) underwent surgery. Among the 131 operated patients at median follow-up of 36 months, 94 (72%) are alive and disease-free. The 5-year DFS and OS were 60% and 77%, respectively. The majority of the failures was distal but with more advanced disease at presentation; both local and distal failures were similar. The outcomes of these patients were similar to world literature, and signet ring cell morphology, pretreatment CEA level, and pathological nodal staging all were influential in determining survival. Besides this, the study highlighted that tumors with signet ring cell morphology appearing in younger population with poor survival need prospective evaluation for more intense conformal radiation therapy (CRT) regimen and aggressive surgical resections as they tend to have poorer outcomes than rest of the population.[24]

Prospective, randomized studies

As poorer outcomes are often observed in patients with locally advanced rectal cancer, which is more common in Indian scenario, most of the research papers and prospective studies have focused on this cohort. A Phase II randomized study from Tata Memorial Centre investigated whether dose escalation could improve resectability in locally advanced rectal cancers. Patients with clinically unresectable rectal cancer were randomized to receive external beam radiation therapy (EBRT) to pelvis (45 Gy) with concurrent oral capecitabine (CRT group; Arm 1) or EBRT to pelvis (45 Gy) alone followed by 20 Gy dose of localized radiotherapy boost to the primary tumor site (RT with boost group, Arm

2). All patients were assessed for resectability after 6 weeks by clinical examination and by CT scan and those deemed resectable underwent surgery. A total of ninety patients were randomized, 46 to Arm 1 and 44 to Arm 2. Eighty-five patients (44 in Arm 1 and 41 in Arm 2) completed the prescribed treatment protocol. Overall resectability rate was low in both groups; R0 resection was achieved in 20 (43%) patients in Arm 1 versus 15 (34%) in Arm 2. Adverse factors that significantly affected the resectability rate in both groups were extension of tumor to pelvic bones and signet ring cell pathology. Complete pathological response was seen in 7% and 11%, respectively. There was greater morbidity such as wound infection and delayed wound healing in Arm 2 (165 vs. 40%; $P = 0.03$). Investigators concluded that escalated radiation dose without chemotherapy did not achieve higher complete (R0) tumor resectability in locally advanced inoperable rectal cancers, compared to concurrent chemoradiation.[25]

Another prospective, double-blind, noncrossover, randomized study investigated the intensification of neoadjuvant chemotherapy (NACT) as an effective downstaging strategy. The study was designed to evaluate whether the capecitabine-oxaliplatin (Cape-Ox) combination was superior to 5-fluorouracil (5-FU)-leucovorin as radio sensitizer for neoadjuvant chemoradiation in downstaging locally advanced rectal adenocarcinoma and to compare the toxicities between the two arms. In Arm A ($n = 21$), patients received capecitabine (1000 mg/m^2 daily) in twice daily dose on days 1–14 and 25–38 and oxaliplatin (85 mg/m^2) intravenous (IV) over 2 h, on days 1 and 29. In Arm B ($n = 21$), patients received leucovorin (20 mg/m^2) and 5-FU (350 mg/m^2) from days 1–5 to days 29–33. Patients in both arms received concurrent radiation (50.4 Gy in 28#, in conventional fractionation of 1.8 Gy per fraction). Six to eight weeks after concurrent chemoradiation, patients underwent assessment and surgery with total mesorectal resection. Postoperatively, adjuvant chemotherapy with m-FOLFOX 6 of 4 months was given to all patients. Objective response rate in Arm A was 80.95% compared to Arm B, which had 66.66% ($P = 0.3055$). pCR rate of Arm A was comparable to Arm B (23.8% vs. 14.28%, $P = 0.6944$). Surgery with R0 resection was possible in 80.95% cases of Arm A compared to 66.66% cases of Arm B ($P = 0.4827$). Grade 3 toxicities were quite comparable between two treatment arms. The authors concluded that intensification of NACT did not improve outcomes in patients with locally advanced rectal cancer.[26]

Audit of impact of time from radiation to surgery

A retrospective study also investigated whether delayed surgery would improve pathological response rates. One-hundred ten patients who completed neoadjuvant chemoradiotherapy (NACTRT) (50 Gy/25 fractions with capecitabine 825 mg/m^2 twice daily) followed by surgical resection were included in the study. For response evaluation, patients were divided into two groups, Group 1 (≤60 days, $n = 42$) and Group 2 (>60 days, $n = 68$). Tumor downstaging, pCR rate, tumor regression grade (TRG), post-NACTRT, and relapse rates were correlated with TRS. Of 110 patients (median age: 49 years [21–73], 71% males; 18 (16.5%) with signet ring histology); 96% patients underwent an R0 resection. On post-NACTRT, CR was attained in 5 (4.5%) patients, partial response (PR) in 98 (89%) patients, and stable disease (SD) in 7 (6.4%) patients. Median time from completion of NACTRT to surgery was 64.5 days (6–474). Median lymph nodes harvested were 10 (1–50). Overall, 22 (20%) patients achieved pCR. A total of 26 (62%) patients in Group 1 compared to 36 (53%) in Group 2 underwent sphincter-sparing surgery (SSS) ($P = 0.357$). Six patients (14%) in Group 1 and 16 (24%) in Group 2 achieved pCR ($P = 0.24$). Median TRG in both groups was three.

The authors concluded that timing of surgery following NACTRT for LA rectal cancer did not influence pathological response, ability to perform SSS or DFS.[27]

Indian Studies on Gastric Cancer

Surgical aspects

Lymphadenectomy in gastric cancer

Patients with locally advanced resectable GCs are increasingly offered NACT following the MAGIC and REAL-2 trials. Shrikhande *et al*. reported on a retrospective analysis of a prospective database of 139 GC patients undergoing radical D2 gastrectomy after NACT over two periods. A comparison was drawn between this group and a cohort of patients undergoing upfront surgery in the same period. Chemotherapy-related toxicity was noted in 32% of patients. Of the 139 patients, 129 underwent gastrectomy with D2 lymphadenectomy, with 12% morbidity and no mortality. Major pathological response of primary tumor was noted in 22 patients (17%). Of these 22 patients, lymph node metastases were noted in 12 patients. The median blood loss and lymph node yield were not significantly different to the 62 patients who underwent upfront surgery. Patients who underwent upfront surgery were older (58 vs. 52 years, $P < 0.02$) and had a higher number of distal cancers (63% vs. 82%, $P < 0.015$) and a longer hospital stay (11 vs. 9 days, $P < 0.001$). The authors concluded that perioperative outcomes of gastrectomy with D2 lymphadenectomy for locally advanced, resectable GC were not influenced by NACT. The number of lymph nodes harvested was unaltered by NACT, but more pertinently, metastases to lymph nodes were noted even in patients with a major pathological response of the primary tumor. The authors, therefore, suggest that D2 lymphadenectomy should be performed in all patients irrespective of the degree of response to NACT.[28]

Radiotherapy and chemoradiotherapy in gastric cancer

There are multiple standards for management of GC ranging from preoperative chemotherapy and radical gastrectomy, D2 lymphadenectomy and adjuvant chemotherapy and D1+ lymphadenectomy and adjuvant chemoradiation and the choice of treatment strategy often depends on the surgical expertise and quality of lymphadenectomy feasible. In Tata Memorial Centre, the standard policy is to offer preoperative chemotherapy followed by D2 lymphadenectomy. Adjuvant chemoradiation is offered to patients who undergo upfront surgery and have locally advanced or node-positive disease on histopathology.

A retrospective analysis of 13 years (1995–2008) of outcomes of patients with GC was performed by the investigators from AIIMS. Of the 69 patients analyzed, a total of 64 had some form of lymph node dissection. Adjuvant

chemoradiation was used in these patients. Of 69 patients treated, 53 patients (76.8%) complied to treatment and all received adjuvant radiation >30 Gy. Of these 53 patients, Macdonald's regimen was used in 49 patients (92.4%). Overall, 9.4% patients (5/53) were hospitalized for supportive care. The median time to recurrence was 14 months. The use of multimodality treatment was associated with improved outcomes.[29]

The use of adjuvant chemoradiation has been questioned after a D2 gastrectomy after the results of ARTIST trial that involved dissection of median of 40+ lymph nodes and randomized patients to systemic chemotherapy with or without adjuvant chemoradiation. While the study did not reveal any superiority of adjuvant chemoradiation, one must note that the study involved essentially Stages I and II disease and D2 surgery was associated with higher nodal yield and node-negative disease. The subgroup of patients with node-positive disease, however, had significant benefit in terms of both DFS and OS.

A study from Tata Memorial Centre had an average nodal yield of 20 lymph nodes with almost 60% nodal positivity, suggesting that most of our patients have advanced disease and may benefit for adjuvant chemoradiation. Till date, there is no randomized comparison of adjuvant chemoradiation versus adjuvant chemotherapy after D2 nodal dissection. While adjuvant chemotherapy alone is an option after D2 gastrectomy, a recent study from Tata Memorial Centre revealed only 64% compliance to preoperative and adjuvant chemotherapy within Indian setting.[28]

A recent study from Tata Memorial Centre that used advanced radiation techniques such as three-dimensional CRT or intensity-modulated radiation therapy (IMRT) revealed <5% GI and <11% hematolymphoid toxicity and compliance of almost 95% suggesting feasibility in Indian patients. The use of adjuvant chemoradiation leads to 38% 3-year survival. Comparative survival data using preoperative or adjuvant chemotherapy alone from India are not available for comparison.[30]

Perioperative chemotherapy

In a retrospective analysis of 99 patients with resectable locally advanced gastro-EC treated with 3 cycles of neoadjuvant and 3 cycles of adjuvant IV epirubicin, oxaliplatin, and oral capecitabine (EOX), 93% patients completed neoadjuvant EOX.[31] On postneoadjuvant chemotherapy, 4 patients progressed, 1 patient died, and 94 were taken up for surgery. Of these, 9 were inoperable and 85 patients underwent radical surgery. Of the operated 85 patients, 71% (60/85) were able to complete three cycles of adjuvant EOX. The compliance to complete all 6 cycles of perioperative chemotherapy was 64%. Grades 3 and 4 toxicities were comparable to the MAGIC dataset apart from the higher number of diarrhea events.

Palliative chemotherapy (first-line)

A retrospective study evaluated 144 patients with advanced GC treated at Tata Memorial Centre.[32] Sixteen patients received best supportive care (BSC), and 128 patients received palliative chemotherapy. Of 128 patients, 42 (33%) received Cape-Ox, 22 (17.1%) EOX, and 47 (36.7%) docetaxel while rest received other regimens. About 97% of patients had ≥3 sites of metastasis. Forty-eight patients (37.5%) had signet ring histology. Median follow-up was 9 months. Median progression-free survival (PFS)/OS was 6/8 months, respectively.

Palliative chemotherapy (second-line)

In the above study, of the 93 patients who progressed, 39 (41.9%) patients received second-line chemotherapy. Multivariate analysis for OS showed that PS and use of taxane in first-line setting were significant prognostic factors. Patients who received second-line therapy had longer survival than those who did not (12 vs. 6 months; $P = 0.002$). The overall outcomes were comparable to the Western reported data despite advanced disease at presentation.[32]

Carcinoma pancreas studies

Role of octreotide in preventing pancreatic fistula

Octreotide helps in decreasing the volume of GI secretions. Whether the administration of octreotide in the immediate postoperative period decreases the incidence of postoperative pancreatic fistula (POPF) has been a matter of debate. Kurumboor *et al*. reported on a randomized controlled trial of 109 patients undergoing elective pancreaticoduodenectomy (PD), with a soft pancreas and a nondilated pancreatic ductal system. On comparing the groups receiving and not receiving octreotide, the rates of significant pancreatic fistula (Grades B and C) were 10.9% and 18.5% (P = ns) and morbidity was 18 and 29.6% (P = ns), respectively. The authors concluded that octreotide does not decrease the rate of pancreatic fistula following PD.[33]

Pancreatic surgery: Technique

Dissection of the uncinate process of the pancreas is a technically challenging surgical step in PD. D'souza *et al*. described a technique of stapler division of the uncinate process in PD. The authors compared 19 consecutive patients who underwent stapler division of the uncinate process to twenty consecutive patients operated without stapler. The overall surgical morbidity in the no-stapler group was 25% (5/20) and 31.6% (6/19) in the stapler group ($P = 0.731$). The mean blood loss in the no-stapler group was 1077.5 ± 594 ml compared to 778 ± 302 ml in the stapler group ($P = 0.113$). The mean operative duration was 498 ± 105 min in the no-stapler group and 490 ± 60 min in the stapler group ($P = 0.773$). The average number of lymph nodes retrieved was 6.1 ± 3 in the no-stapler group versus 5.9 ± 4 in the stapler group ($P = 0.627$). Neither group had positive resection margins. The authors concluded that stapler division of the uncinate process for selected periampullary tumors compared well with the conventional method had comparable perioperative outcomes without compromising oncological radicality and had the potential to simplify uncinate resection.[34]

Bulky tumors in the pancreatic head and primary tumors in the uncinate process posed a particular surgical challenge due to the proximity to the root of the superior mesenteric artery (SMA). Various surgical approaches had been described to approach the SMA early during PD to enable an early evaluation of operability in these cases.[35] Shrikhande *et al*. reported on a comparative analysis between thirty patients undergoing a combined uncinate process – SMA first approach (Group 1) and 14 patients undergoing a conventional uncinate process first approach (Group 2) in PD. Median intraoperative blood loss in Group 1 was 800 ml while that in Group 2 was 600 ml. A mean

of 0.52 units of blood was transfused in Group 1 (range 0–3) compared to 0.2 units in Group 2 (range 0–1). The median operative time in Group 1 was 457.5 min and the median operative time was 450 min in Group 2. Complication rate was 40% and 14.3% in Groups 1 and 2, respectively. Median duration of hospital stay was 14 days in Group 1 and 12.5 days in Group 2. Median nodes resected in Group 1 were 8 (range 0–26) while in Group 2 they were 9 (range 2–14). Resection margins were positive in two cases (one in each group). There were two mortalities in Group 1 and no mortalities in Group 2. None of the above differences were statistically significant. The authors concluded that the SMA first is a safe technique. It compares well with the uncinate first approach in terms of operative time, blood loss, number of lymph nodes retrieved, margin positivity, and operative morbidity. Both techniques may be useful in situations such as a large uncinate process tumor or when superior mesenteric vein/portal vein/SMA involvement is suspected or present.[36]

Pancreatic surgery: Standardization and service reconfiguration

Shrikhande *et al*. reported on the largest series on perioperative outcomes for pancreatoduodenectomy from Southwest and South Central Asia - a region with a low incidence of PC and a disproportionate distribution of resources, highlighting the impact of high volumes, standardization and service reconfiguration. Five-hundred PDs were performed with a morbidity and mortality rate of 33% and 5.4%, respectively. Three specific time periods marking major shifts in practice and performance of PD were identified, namely, periods A (1992–2001; pancreaticogastrostomy predominantly performed), B (2003-July 2009; standardization of pancreaticojejunal anastomosis), and C (August 2009–December 2011; introduction of NACTRT and increased surgical volume). Over the three periods, volume of cases/year significantly increased from 16 to 60 ($P < 0.0001$). The overall incidence of POPF/pancreatic anastomotic leak, hemorrhage, delayed gastric emptying, and bile leak was 11%, 6%, 3.4%, and 3.2%, respectively. The overall morbidity rates, as well as the above individual complications, significantly reduced from period A to B ($P < 0.01$), with no statistical difference between periods B and C. The authors concluded that the evolution of practice and perioperative management of PD for PC at their center improved perioperative outcomes and helped sustain the improvements despite increasing surgical volume.[37]

Pancreatic cancers: Radiotherapy aspects

A prospective Phase II study investigated the role of neoadjuvant gemcitabine-based chemoradiation for borderline resectable PCs. The results were presented in abstract form and authors had reported 26% resectability rate.[38]

Gallbladder Cancer

Resectability following neoadjuvant chemotherapy

Although rare over most of the world, gallbladder cancer (GBC) is very common in Northern India. Selvakumar *et al*. reported on the efficacy of NACT in a locally advanced GBC in terms of resectability rates.[39] Of the 21 patients deemed resectable after NACT in this study, 66.67% could undergo an R0 resection. The mean OS in patients with an R0 resection was 42.8 months versus 6.6 months in patients with unresectable disease. The authors concluded that NACT improves resectability in some patients with unresectable GBC and that resection after NACT is feasible and may improve survival in a select group of patients.[39]

Surgical approach for radical cholecystectomy

Laparoscopic surgery has traditionally been contraindicated for the management of GBC. Agarwal *et al*. reported on a retrospective comparative analysis between 24 patients who underwent a laparoscopic radical cholecystectomy (Group A) and 46 matched controls who underwent open surgery (Group B). The median operating time was higher in Group A (270 vs. 240 min, $P = 0.021$) and the median blood loss (ml) was lower (200 vs. 275 ml, $P = 0.034$). The postoperative morbidity and mortality were similar ($P = 1.0$). The median lymph node yield was 10 (4–31) and was comparable between the two groups ($P = 0.642$). During a median follow-up of 18 (6–34) months, one patient in Group A and 3 in Group B developed recurrence. No patient developed a recurrence at a port site. The authors concluded that laparoscopic radical cholecystectomy is safe and feasible in selected patients with GBC.[40]

Staging laparoscopy in gallbladder cancer

Agarwal *et al*. reported on the role of staging laparoscopy (SL) in the management of GBC in a prospective study of 409 patients. Of the 409 primary GBC patients who underwent SL, 95 had disseminated disease (surface liver metastasis [$n = 29$] and peritoneal deposits [$n = 66$]). The overall yield of SL was 23.2% (95/409). Of the 314 patients who underwent laparotomy, an additional 75 had unresectable disease due to surface liver metastasis ($n = 5$), deep parenchymal liver metastasis ($n = 4$), peritoneal deposits ($n = 1$), nonlocoregional lymph nodes ($n = 47$), and locally advanced unresectable disease ($n = 18$), that is, 6-DL and 69-UDL. The accuracy of SL for detecting unresectable disease and DL was 55.9% (95/170) and 94.1% (95/101), respectively. Compared with early GBC, the yield was significantly higher in locally advanced tumors ($n = 353$) (25.2% [89/353] vs. 10.7% [6/56], $P = 0.02$).[41]

Gallbladder cancer and radiotherapy

While a recent surveillance, epidemiology, and end results report supports the use of adjuvant chemoradiation for locally advanced GBC in addition to systemic chemotherapy, the current consensus recommendations do not include adjuvant or radical chemoradiation as a standard treatment.

Adjuvant chemoradiation

In 2006, investigators from Tata Memorial Center published outcomes of sixty patients treated with adjuvant radiation. On histopathological staging, 28 patients (46.5%) had Stage II, 19 (32%) had Stage III, 12 (20%) had Stage I, and one patient had Stage IV disease. Thirteen (21%) patients did not receive any adjuvant treatment, 32 (53%) patients received adjuvant RT alone, 8 (14%) received postoperative CT + RT, and 7 (12%) patients received CT alone. With a median follow-up of 18 months (12–124 months), 27 (45%) patients were disease-free, 11 (19%) had local failures, 7 (11%) had locoregional, 7 (11%) had locoregional and distant, 4 (7%) had distant, and 4 (7%) had local and distant failures. The overall DFS and OS were 30% and 25%, at 5 years, respectively. Stage grouping ($P = 0.007$) and pathological T ($P = 0.01$) had significant impact on DFS on univariate

analysis whereas histological grade (P = 0.06) showed trend toward significance.[42]

More recently, investigators from Sanjay Gandhi Post Graduate Institute (SGPGI) reported on outcomes of 32 patients treated with adjuvant chemoradiation. Of the 32 patients who received treatment at a median follow-up of 53 months, 40% of patients had recurrence either locoregionally (12%) or had distant metastases (28%). The 5-year OS and DFS were 53% and 25%, respectively. When prognostic factors were evaluated, the median OS was 51 versus 23 months for node-negative versus node-positive disease, not reached versus 34 months for Stage I versus Stage III, 46 versus 23 months for R0 versus R1 resection, 51 versus 12 months for well-differentiated versus poorly differentiated tumours (n = 8), and 51 versus 10 months for lymphovascular invasion. Authors concluded that adjuvant concurrent chemoradiation therapy followed by AC improves outcomes in patients with R1 and node-positive disease. Advanced stage, nodal positivity, poor differentiation, and presence of perineural invasion and lymph vascular invasion are adverse prognostic features.[43]

Radical chemoradiation

Radical chemoradiation is often offered to patients whose disease is not amendable to curative resection and is often considered a palliative approach. A recent observation report from Tata Memorial Centre reported metabolic and pCR in three patients undergoing chemoradiation for GBC. Preoperative chemoradiation consisted of gemcitabine at 300 mg/m^2 weekly and use of IMRT to a dose of 57 Gy in 25 fractions to the gross tumor and 45 Gy in 25 fractions to the clinical target volume to cover the areas of microscopic spread. Complete metabolic and radiologic response was observed in two patients and PR in one patient. Two patients underwent complete surgical excision, of which one patient had complete pathological response and one patient had small residual tumor in the primary and no nodal metastasis. The third patient could not undergo surgery due to medical reasons.[44]

These observations led to initiation of Phase II prospective study that uses neoadjuvant chemoradiation for downstaging locally advanced disease. Long-term results of this trial reported that up to one-third of patients could become long-term survivors after downstaging followed by radical surgery albeit with increased biliary tract complications.[45]

Recent data from Tata Memorial Center also demonstrated feasibility of downstaging with NACT alone and a randomized trial is envisaged to test the most effective neoadjuvant downstaging strategy in locally advanced nonmetastatic tumors.

Chemotherapy and Gallbladder Cancer

Neoadjuvant chemotherapy studies

A retrospective study evaluating the outcome of 37 patients treated with locally advanced GBC treated with gemcitabine- and platinum-based regimen as NACT reported that an overall response rate was 67.5%. Seventeen patients (46%) underwent R0 resection. Median OS/PFS of the whole group was 13.4/8.1 months, respectively. Patients who underwent surgery had a significantly better OS (median not reached vs. 9.5 months) and PFS (25.8 vs. 5.6 months), respectively.[46]

Palliative chemotherapy

An RCT (Randomized Control Trial) to evaluate efficacy of modified gemcitabine and oxaliplatin (mGEMOX) over BSC or FU and folinic acid (FA) in unresectable GBC randomly assigned 81 patients to three arms: BSC; IV 5-FU and FA weekly bolus for 30 weeks; and mGEMOX IV every 3 weeks.[47] CR plus PR in the three groups was zero (0%), four (14.3%), and eight (30.8%), respectively (P < 0.001). Two patients in the mGEMOX arm and one patient in the FUFA arm underwent curative resection after chemotherapy. One patient in the mGEMOX arm had complete pathologic response. Median OS was 4.5, 4.6, and 9.5 months for the BSC, FUFA, and mGEMOX arms (P = 0.039), respectively. PFS was 2.8, 3.5, and 8.5 months for the three groups (P < 0.001), respectively. There was no difference in Grade 3/4 toxicities in the chemotherapy arms except transaminitis, which was more prevalent in mGEMOX arm (P = 0.04). Two patients in the FUFA arm and ten patients in the mGEMOX arm had Grade 3 or 4 myelosuppression, respectively. Two patients in the mGEMOX group had neutropenic fever that resolved with antibiotics. This randomized controlled trial confirmed the efficacy of chemotherapy (mGEMOX) compared with BSC and FUFA in improving OS and PFS in unresectable GBC.

A Phase II study planned to determine the response rates of the gemcitabine and cisplatin (GemCis) combination in 30 unresectable GBC patients reported were 4 (13.3%) complete responders, 7 (23.3%) partial responders, and 7 (23.3%) with SD, with 4 (13.2%) patients showing disease progression.[48] The median time to progression was 18 weeks (95% confidence interval [95% CI]: 14–24 weeks), and the median duration of response was 13.5 weeks (range 5.5–104 weeks). The median OS was 20 weeks (95% CI: 14–31 weeks), with 1-year survival rate of 18.6%. The regimen was well-tolerated with Grade 3 or 4 anemia seen in seven (23.3%) and four (13.3%) patients, respectively. Five (16.6%) patients each experienced Grade 3 or 4 neutropenia, and Grade 3 or 4 thrombocytopenia was seen in three (10%) and two (6.6%) patients, respectively.

Another Phase II study designed to evaluate efficacy of gemcitabine and oxaliplatin combination in unresectable GBC enrolled fifty patients, of which 48 were analyzed.[49] Response rates were CR 3 (6.2%), PR 7 (15%), SD 17 (35.4%), and PD 18. One had complete pathological response. Median OS and PFS were 7.5 and 3 months, respectively. OS in responders was 10.5 versus 4 months in nonresponders (P < 0.0000). Eleven patients (23%) survived for a year or more. There were no toxic death and Grade 3/4 toxicity seen in 10 (22%) patients: diarrhea 3, vomiting 2, and neutropenia and thrombocytopenia 5 patients.

A study evaluated the impact of relative total dose intensity (RTDI) on clinical benefit among 121 patients with locally advanced inoperable carcinoma gallbladder receiving GemCis chemotherapy.[50] RTDI of at least 50% conferred substantial clinical benefit compared to lower RTDI (75.49% vs. 21.05%). RTDI above 50–59% did not improve clinical benefit. Subsequently, extended cholecystectomy rates did not significantly improve among patients who received RTDI >50–59%. Significantly higher neutropenia and anemia of at least Grade 2 occurred with RTDI >70% versus RTDI 50–59%. The authors concluded that an RTDI of chemotherapy higher than 60% among patients with inoperable locally advanced carcinoma gallbladder conferred no significant improvement in clinical benefit and subsequent rates of

extended cholecystectomy. Higher RTDI, however, led to significantly increased toxicity among these patients.

A retrospective analysis evaluated 210 patients with advanced GBC treated with gemcitabine-platinum combination.[51] A total of 158 patients had metastatic and 52 had locoregional disease. Median number of cycles was 5 (1–12). At a median follow-up of 10 months, median OS/PFS was 10/5 months, respectively. On multivariate analysis, patients who underwent prior surgery for primary and locoregional disease had a significantly better PFS and those with locoregional disease had a significantly better OS. About 45.7% received second-line chemotherapy. The use of gemcitabine-platinum combination in Indian patients showed slightly worse outcomes possibly suggesting an aggressive biology.

In another prospective study, 65 patients with inoperable GBC received palliative chemotherapy with CDDP and 5-FU.[52] A total of 19 patients had locally advanced unresectable cancer and 46 patients had metastatic cancer. A total of 212 chemotherapy cycles were administered to the patients. Response evaluation after three cycles of chemotherapy revealed CR in five patients (7.69%; 95% CI: 2.87–16.22), PR in 17 patients (26.15%; 95% CI: 16.57–37.81), stabilization of disease in nine patients (13.85%; 95% CI: 6.96–23.88), and progression in 21 patients (32.30%; 95% CI: 21.80–44.35). At 6 months, 44.6% patients were alive and 18.5% patients were alive at 12 months. The median OS was 5.7 months and the median time to disease progression was 3.1 months. This chemotherapy combination was well-tolerated. There were no chemotherapy-related deaths. Infusion chemotherapy with CDDP and 5-FU had a fair amount of activity in patients of inoperable GBC, with acceptable toxicity. Tumor shrinkage following treatment with this regimen enabled surgical resection in two patients.

Biliary Tract Cancers

Radiotherapy studies in biliary tract cancers

Ampullary cancers

A retrospective study from SGPGI hospital evaluated outcomes regarding adjuvant chemoradiation in patients with ampullary cancer. Of the 113 patients who underwent PD, 49 received adjuvant chemoradiation (median dose 50.4 Gy with concurrent 5-FU). The long-term outcome was compared with patients who did not receive adjuvant chemoradiation (n = 55). The overall median survival was 30.1 (range 1.6–140.0) months with actuarial 1-, 3-, and 5-year survival rates of 79%, 43%, and 33%, respectively. No significant difference in median survival (34.6 vs. 24.5 months; P = 0.3) and actuarial 5-year survival rates (38 vs. 28%) was seen between those who received and those who did not receive adjuvant therapy. Adjuvant chemoradiotherapy did not influence the survival in high-risk (HR) patients (P = 0.84), in various T and N stages and had no impact on locoregional recurrence (P = 0.6).[53]

Unresectable cholangiocarcinoma

A retrospective study from Tata Memorial Centre evaluated the outcomes of patients with unresectable Klatskin's tumors with endobiliary brachytherapy with or without external beam concurrent chemoradiation. High-dose concurrent chemoradiation (gemcitabine-based) with endobiliary brachytherapy lead to median survival of 16 months, which is more than that with doublet systemic chemotherapy alone.[54]

Another study using stenting and endobiliary brachytherapy for Type II malignant strictures revealed improvement in survival with the use of endoluminal brachytherapy as compared to endoluminal stenting alone (225 vs. 100 days, P = 0.02).[55]

Anal cancer

Concurrent chemoradiation followed by salvage surgery (APR) constitutes the present standard of care for patients with early and locally advanced anal cancer.

Both AIIMS and Tata Memorial Centre published the outcomes following concurrent chemoradiation in 2005.

AIIMS reported on outcomes of forty patients with squamous cell carcinoma of anal canal who received 2 cycles of NACT (cisplatin and methotrexate) followed by chemoradiation. A vast majority of these patients (87%) were locally advanced. At a median follow-up of 60 months, OS, DFS, and colostomy-free survival were 80%, 77.5%, and 72.5%, respectively.[56] An updated report from AIIMS that included 47% locally advanced patients reported an eventual sphincter preservation rate of 26.5%, which is much lower than almost 50% rate reported in key, randomized studies of chemoradiation.[57]

An outcome report of 16 patients treated with combination of external radiation and chemotherapy followed by interstitial brachytherapy has been reported by PGI. With a median follow-up of 41 months (range, 20–67.2 months), preservation of the anal sphincter was achieved in 14 patients. The 1- and 2-year local control rates were 93.8% and 87.5%, respectively.[58]

The outcomes of a larger cohort (n = 257) were reported by Tata Memorial Centre. In Tata Memorial series, none of the patients received NACT. Patients with T1–T2 tumors who received the radiation dose between 55 and 60 Gy and those with T3–T4 received 65 Gy with a select group within this cohort receiving boost through interstitial brachytherapy. All patients received concurrent 5-FU and mitomycin-based chemotherapy. Although these doses are higher than international recommendations, the investigators clearly demonstrated dose-response relationship with higher doses associated with improved local control, especially in T3–T4 tumors. The 5-year OS and DFS for the whole group were 71.5% and 61%, respectively.[59]

Hepatocellular carcinoma

There are no data regarding the use of sorafenib except for some case reports on toxicity.

Palliative chemotherapy

A single-center retrospective experience of the use of gemcitabine in combination with cisplatin in 24 patients with HCC receiving three or more cycles of chemotherapy reported six (25%) patients to have a PR and an additional 12 (50%) to have SD.[60] The median OS was 7.5 months (95% CI: 4.5–10.5 months) and 1-year survival was 18%. The toxicity profile was acceptable. Grades 3 and 4 anemia, thrombocytopenia, and neutropenia were observed in 17%, 17%, and 33% patients, respectively. The most frequent nonhematologic toxicities were nausea and vomiting and peripheral neuropathy.

Another study which was planned to determine the response rates of a combination of GemCis in thirty unresectable

HCC in Indian patients reported 6 (20%) patients achieving a PR and 13 (43%) demonstrating SD with 11 (37%) patients showing disease progression.[61] The median time to progression was 18 weeks (range 1–74 weeks) and the median duration of response was 13 weeks (range 4–68 weeks). The 1-year survival rate was 27% and the median OS was 21 weeks (95% CI: 17–43 weeks). This regimen was well-tolerated. The WHO Grades 3 and 4 anemia was seen in 11 (37%) and 2 (7%) patients, respectively. Four (13%) patients each experienced Grades 3 and 4 neutropenia, and Grades 3 and 4 thrombocytopenia was seen in 2 (7%) patients each. Major, nonhematologic toxicities were Grade 4 elevated bilirubin levels and Grade 3 oral toxicity, in one patient (3%) each.

Gastrointestinal Stromal Tumors

The Indian literature regarding gastrointestinal stromal tumors (GISTs) comprises many case reports and some single center experiences.

Neoadjuvant imatinib

A study on 29 patients, who were administered neoadjuvant imatinib for borderline resectable and locally advanced GISTs followed by surgery, reported median duration of neoadjuvant imatinib administration to be 8.5 months.[62] The response rate with neoadjuvant imatinib was 79.3%. Five patients, initially considered to have locally unresectable lesions, ultimately underwent resection (three R0, two R2). Another three patients, who had M1 disease, underwent R2 resection (due to the presence of metastasis) with complete resection of the primary lesion. Nineteen patients, who would have originally required extensive surgery, underwent conservative surgery (R0). In two patients, neoadjuvant imatinib did not influence the final procedure. The postoperative complication rate was 13.8%, and there were no postoperative deaths. There were one locoregional recurrence and two cases of distant metastasis. The 1-, 2-, and 3-year OSs were each 100%.

In a study from East India, on 19 patients with locally advanced GIST, 13 achieved PR and 6 with stable response on preoperative imatinib. Histopathological evaluation and grading of responses revealed only moderate- and low-grade pathological response after imatinib. R0 resection was possible in 13/19 and R1 in 6/19 patients.[63] Imatinib was well-tolerated and adverse reactions were minimal. Postoperative complications of surgery were not out of the ordinary for a surgical series featuring extensive abdominal surgery.

In a study on six patients, with locally advanced GISTs, who received oral imatinib 400 mg daily, for a median period of 3.5 months (range 1–20 months), the median reduction in the tumor volume was 40% (range 20–50%).[64] Four of the six patients underwent successful complete resection of the tumor and were disease-free after a median follow-up of 10.5 months (range 3–20 months). Imatinib did not produce serious toxicity in any patient.

Another study on preoperative use of imatinib in ten patients with operable advanced and metastatic GIST also reported 45% (range 20–60%) median reduction of tumor volume.[65] Six of ten patients underwent complete resection of the tumor following neoadjuvant imatinib for a median period of 3 months and were disease-free for a median follow-up of 11 months (range 6–24 months). Imatinib did not produce serious toxicity in any patient.

Adjuvant imatinib

In a retrospective study on 113 GIST patients, 70% patients had HR category as per Fletcher risk score.[66] About 53% had curative resection, after which 34% had adjuvant imatinib therapy. Recurrence rates were significantly lower in patients receiving adjuvant imatinib therapy ($P = 0.003$). No statistically significant association was noted between HR Fletcher score, Mib score > 10, tumor size > 10 cm, and the risk of recurrence ($P = 0.29$, 0.07, and 0.87, respectively). Liver was the most common site of metastasis. Side effects were tolerable, and edema and fluid retention were most common.

A retrospective study of cases encountered over a 7-year period (1999–2005) evaluated 92 cases of GIST. About 70.4% patients were of the HR malignant category.[67] Follow-up of 11 cases, the majority with HR tumor, treated with adjuvant imatinib for 6 months after surgical resection showed SD for periods from 2 to 5 years. However, 11 cases treated with imatinib for longer than 6 months had a poorer outcome due to recurrent, metastatic, or inoperable disease.

Adjuvant/palliative imatinib

A 5-year retrospective analysis reported 49 patients treated for GIST.[68] Imatinib was administered after surgery in patients with HR, residual or metastatic disease and at onset of recurrence or metastatic disease in patients with intermediate risk. At a median follow-up of 21 months, 2- and 3-year recurrence or PFS rates were 61 and 39%, respectively, for all patients. The median recurrence-free survival rates in the intermediate-risk and HR groups were 7 and 49 months, respectively. The median PFS in the residual and metastatic group was 10 and 29 months, respectively, although the number of patients was small.

A retrospective series of short-term experience with 50 cases of GIST showed 30 (60%) patients had complete resection of tumor with median PFS of 12 months.[69] The difference in PFS between intermediate and HR groups was significant for patients who underwent resection ($P = 0.016$). Thirty-five patients with advanced disease were administered IM 400 mg daily, and CR was noted in 4 (11.8%); 13 (38.2%) each had PR and SD, and 5 (14.8%) had progressive disease. Responses were not different in groups based on sex, site of primary tumor, and number of metastatic sites. At a median follow-up of 10 months, 72% patients continue to maintain the response.

Neuroendocrine tumors

There is only one published Indian study of a single-center experience of 74 gastroenteropancreatic-neuroendocrine tumors seen over 7 years, which did not give outcomes.[70] Most other reports from India have been case reports or smaller case series.[71]

Other sites of tumors

There are no studies from India focusing on chemotherapy of gastrointestinal melanomas, anal canal cancers, CRCs, pseudomyxoma peritonei, small bowel adenocarcinomas, and periampullary cancers except for a few case reports or small case series.

Discussion and Conclusion

The present study has elucidated treatment outcomes in gastrointestinal cancers in Indian population. Considering GI cancers, a heterogeneous disease with site-specific treatment options and variable outcomes, the overall data and outcomes are extremely variable. As suggested, most of the studies are

small ones and retrospective analyses. While one has to be careful in interpreting the data and the outcomes, these data can be used to calculate the disease burden and plan sample size for large prospective studies. Young patients with pathology unique to the Indian subcontinent (for example, signet ring rectal cancer, GBCs) suggest solution for such pathology needs to come from the Indian continent itself. Joint efforts to improve outcomes for GI cancer can be integrated under the national cancer grid program.

Positive way forward should be to have mutlicentric randomized trials in GI cancers to have more robust inferences, which can be applied specifically to the Indian population.

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Conflicts of interest

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