To conclude, these two randomized studies show the superiority of CTC over barium enema for detection of colon cancer and large polyps in symptomatic patients. The second trial shows equal efficacy of CTC compared with colonoscopy in detecting colorectal cancer but with a higher need for additional colonoscopy. Though CTC has been found equivalent to colonoscopy, the verdict is not still out whether CTC is to be recommended over colonoscopy in symptomatic patients.

The implications of this trial are not clear for India and other countries with a low prevalence of colorectal cancer and where screening programmes are not in place. In India, the ground reality is that CT scan machines are not accessible or affordable for most of the population. Moreover, colonoscopy costs half as much as CTC; it can detect, sample as well as allow therapy (polypectomy) in a single setting. Also, it obviates the need for a second investigation which may be required in patients who have undergone CTC as the first investigation. Moreover, the expertise to interpret CTC is still in the nascent stage and no standardized protocols have been developed. Thus, the sensitivity and specificity of CTC may be lower at most centres in India compared with the West. A standardized evaluation protocol as well as training of endoscopists are required to ensure the effective use of colonoscopy. In India, barium enema may still be a realistic diagnostic option for patients with symptoms suggestive of colorectal cancer due to the availability of equipment and expertise.

With advances in the field of colonoscopy in the form of water immersion technique to reduce patient discomfort, image enhancement with chromoendoscopy, narrow band imaging, confocal endomicroscopy, endocytoscopy for higher cancer detection rates at an earlier stage, colonoscopy will continue to challenge CTC despite it being a non-invasive procedure. CTC would be a useful option for those with incomplete colonoscopy. The emerging role of colon capsule endoscopy may change the way we look at this issue by the end of this decade.

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Tumour size and lymph node metastases as prognostic markers of pancreatic cancer: Old lessons revisited

Tummala P, Howard T, Agarwal B. (Division of Gastroenterology and Hepatology, St Louis University School of Medicine; and Missouri Baptist Medical Center, St Louis, Missouri, USA.) Dramatic survival benefit related to R0 resection of pancreatic adenocarcinoma in patients with tumor ≤25mm in size and ≤1 involved lymph nodes. *Clin Transl Gastroenterol* 2013;**4:**e33.

SUMMARY

This retrospective study by Tummala *et al*. aimed to analyse the impact of a complete (R0) resection, size of the tumour and peripancreatic lymph node metastases on survival in patients undergoing upfront surgery for pancreatic cancer. The authors divided their cohort of 154 patients treated over 10 years into those who underwent a complete curative or R0 resection (*n*=105 or 68%) and those in whom the pathological examination of the resection margin revealed the presence of cancer or R1 resections (*n*=49 or 32%).

While the overall median survival of the study subjects was 24.1 months, patients who underwent an R0 resection had a median overall survival of 26.8 months while those who underwent an R1 resection had a median overall survival of 17.7 months (p=0.01). On the other hand, patients who had no lymph node metastasis had a statistically significant benefit compared to patients with even a single lymph node metastasis (34.8 *v*. 19.9 months; p=0.014). Using Cox-proportional hazards regression analysis, the authors pin-pointed tumour size (>25 mm) and lymph node metastasis to two or more lymph nodes as the two most significant factors that negatively impact on survival despite an R0 resection. The authors indicate that their data regarding patients with tumours >25 mm and/or metastasis to two or more lymph nodes whom they suggest should be grouped under the 'borderline resectable cancers' raises a couple of questions: should this subset of patients be considered for neoadjuvant therapy or for no treatment at all?

COMMENT

While the paper is well written and packed with survival curves, the factors analysed do not appear to be new to the literature. The influence of the size of tumour on the outcome of pancreatic cancer is not new. Bittner *et al*.,[1] as early as 1989, suggested that only patients in TNM stage I benefited from a surgical resection. However, to date, the world literature[2–6] strongly agrees that surgery remains the only chance of cure in resectable pancreatic cancer.

Tummala *et al*. infer from their data that surgery alone does not provide cure even if an R0 resection is performed in tumours >25 mm and more than 1 positive lymph node, and thus these patients may need to undergo neoadjuvant chemotherapy. There is merit in the argument proposed by the authors regarding the consideration of neoadjuvant chemotherapy in patients with larger tumours. However, neoadjuvant chemotherapy in pancreatic cancer has been administered as a downstaging modality for a little more than a decade, albeit in small series.[7] While the results from the scattered series on neoadjuvant chemotherapy in patients with locally advanced cancer and those in whom an R0 resection may not be feasible at the outset may seem encouraging, the suggestion from the authors that these neoadjuvant therapies may need to be considered in resectable lesions >25 mm with or without 2 or more positive lymph nodes seems largely academic because there is no convincing evidence based on a critical review of the literature.[8]

Towards the end of the discussion, the authors seem to deviate from their initial 'evidence-based' approach to make a generalization followed by a contentious statement: 'If upfront surgery with R0 resection does not confer survival benefit versus R1 resection, two questions then arise: (i) is there any survival benefit with surgery compared with similar staged patients who are not operated upon.' It is ironic they make such a statement given that their own data indicate a benefit/survival advantage in patients who underwent an R0 resection albeit in tumours <25 mm and with <2 lymph nodes involved. While the available data are very clear when it comes to the lack of benefit of planned R2 resections on the overall outcome,[9] not offering surgical resection to a patient with a resectable cancer who is fit to undergo surgery in the present day and age would be bordering on 'blasphemy'. While there are few 'non-believers' in surgery, who would argue that there exists no 'randomized trial' to conclusively prove the benefit of surgery over no surgery, the ethical standpoint remains: 'Do we even need a randomized trial to answer this question?' Even if an ethics committee clears such a trial, it would be interesting to see how many patients would actually volunteer to be a part of that trial. There is ample evidence from large cohorts of patients documenting the benefit of surgery versus no surgery in localized pancreatic cancer.[10,11] Besides, improvements in surgical technique and critical care have enabled a dramatic reduction in the morbidity and mortality of patients undergoing pancreatic surgery over the past few decades, thereby making safe pancreatic surgery widely available. A recent randomized trial from Japan has even shown that radiochemotherapy cannot be considered an alternative to surgery in locally invasive pancreatic cancer.[12]

The authors appear to have stretched the highlight for their paper a little too far when they concede in the first line of their discussion that margin-negative resection (R0), tumour size and lymph node status are known to be significant determinants of postoperative survival following upfront surgical resection in patients with pancreatic cancer; yet in the very next line they justify their study by stating that the 'relative importance of these factors in predicting survival benefit with surgery, however, has not been clearly established'.

Besides the above, closely examining the data reveals the following: the authors appear to have misinterpreted their own statistics in the case of lymph node metastasis. The data presented by the authors indicate that there is no statistically significant survival benefit even if a single lymph node is involved (p=0.068) rather than their inference that two or more lymph nodes confer poor survival. This, too, is in keeping with the published literature[13]––an appreciation of which led the authors of the seventh edition of the American Joint Cancer Committee TNM staging in 2010 to alter their definition of N1 disease (indicating even a single positive lymph node). Another observation that seemed out of line was why a patient with a head/uncinate process mass underwent a distal pancreatic resection.

In the end, the take-home message based on an objective review of the authors presented data is that tumour size may be a useful criterion to guide decision-making when planning trials comparing neoadjuvant chemotherapy followed by surgery versus upfront surgery followed by adjuvant treatment. We suggest that such treatment strategies should be used only within the confines of randomized trials.

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