

# Adopting Postoperative Chemoradiotherapy in Resected Gastric Cancer

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**E**nestvedt and colleagues have reported in this issue of *GCR* a population-based analysis of surgical procedures and adjuvant therapy used in resectable gastric cancer.<sup>1</sup> Data from the Oregon State Cancer Registry were used to assess the treatment of gastric cancer before and after 2001, when the results of INT116,<sup>2,3</sup> a phase III study of postoperative chemoradiotherapy (CRT) in resected gastric cancer patients, showed that postoperative CRT improved both disease-free and overall survival after gastrectomy. Postoperative CRT has been accepted as a standard of care for patients undergoing gastrectomy for stage IB-IV(M0) adenocarcinoma.<sup>2,3</sup>

The major question asked by Enestvedt et al was whether the positive results from INT116 influenced the patterns of care of resected stomach cancer in Oregon. Three hundred eight patients diagnosed with stomach cancer met the Oregon study inclusion criteria of resected stage IB-III gastric cancer. Use of adjuvant CRT was analyzed in these cases. Before 2001, postoperative treatment was used in 17% of the Oregon cases. After 2001, use of postoperative treatment more than doubled, to 36.8% of cases. This increase was statistically significant ( $P < .001$ ). The increased adoption of improved therapy is encouraging. However, almost two thirds (63.2%) of eligible cases did not receive appropriate postoperative adjuvant therapy, even though the results of INT116 were widely publicized.

In looking at the use of postoperative CRT in the Oregon population-based sample, two findings are striking. First, patients enrolled in INT116 had better survival outcomes than did patients matched for stage and risk factors in the Oregon cohort. In stage IB-III patients undergoing CRT, the differences were 20 months for Oregon cases vs. 36 months for INT116 cases. In patients not receiving postoperative CRT, the median survivals were 15 months vs.

27 months for Oregon and INT116 cases, respectively, indicating that INT116 patients who received surgery alone had better outcomes than Oregon surgery-only patients. The second striking finding is that postoperative CRT, the new standard of care, was not used in close to two thirds of cases in Oregon.

Enestvedt and colleagues discuss several reasons why the outcomes of Oregon cases receiving CRT are worse than those of similar cases on INT116. It is not surprising that patients in a clinical trial do better than similar patients not treated on a study. Patients enrolled in any clinical trial comprise a "special" subset of all cases. Selection to be approached for clinical trial participation may represent a clinical bias that a patient is in "better" general condition.

Patients enrolling in a study must be able to meet all the frequently demanding eligibility criteria for trial participation. For example, INT116 cases had to be able to initiate therapy on a trial of complex upper abdominal CRT within 54 days of gastrectomy. They had to have good performance status (the vast majority were Eastern Cooperative Oncology Group PS 0 or 1), and they had to be alimenting themselves at  $>1,500$  Kcal per day.

Clinicians with experience in gastric cancer patient management know that postoperative cases capable of meeting these criteria are intrinsically healthier patients who would be expected to tolerate therapy well and experience better outcomes than sicker postoperative patients. Thus, some outcome differences between the Oregon and INT116 cases could be explained by the fact that INT116 cases are highly selected.

Another difference between the Oregon and INT116 cohorts pertains to radiotherapy quality control. The upper abdominal CRT delivered in INT116 is complex and requires sophisticated radiation equipment in the hands of experienced radiation

oncologists. In INT116, all radiation treatment plans were centrally reviewed for accuracy.<sup>3</sup> One third of the treatment plans were incorrect and required major changes. Two thirds of these plans would have undertreated areas at risk for tumor relapse. One third of the plans would have been dangerously toxic, typically by irradiating too much liver, kidney, or heart tissue. We have no information on radiotherapy quality control in the Oregon cases.

Other major issues that may influence outcomes in gastric cancer are the presence of tumor in resection margins and lymph node involvement. The INT116 trial mandated careful pathology review, and no patients were enrolled who did not have documented R0 resections. In the Oregon patients, cases having R1 resections on the basis of tumor-positive resection margins were included in the study group. These patients do worse than R0 cases.<sup>4</sup>

Another important factor related to survival in gastric cancer is assessment of lymph node metastases. Bunt et al,<sup>5</sup> in the context of the Dutch<sup>6</sup> phase III trial of D1 vs. D2 surgical resection, convincingly demonstrated that adequate staging requires a full assessment of N1 and N2 lymph nodes. In Bunt's study, the pathology of stomach cancer cases undergoing D2 gastrectomy were assigned a tumor stage by initially evaluating only the N1 nodes. Subsequently, the N2 nodes were examined and the final stage was assigned. The evaluation of N2 nodes increased stage. For example, 60%–75% of cases with stage-III disease went to stages IIIB or IV. These results confirm that examining a large number of nodes is mandatory for adequate staging.

It should be noted that about 70% of the Oregon patients had less than 15 nodes examined, making the staging data in these cases suspect. It is also important to note the INT116 trial also staged cases poorly, but since the clinical trial was

prospectively randomized, the number of inadequately staged cases should be balanced between the CRT and control arms of the study.

Recently, a 10-year follow-up of INT116 was presented. This report provided one result that altered the current understanding of efficacy of postoperative CRT.<sup>2</sup> Exploratory subset analysis of tumor differentiation and outcome strongly suggests that cases with poorly differentiated diffuse pathology did not benefit from CRT, whereas cases with intestinal-type histology did benefit. This is important with regard to the outcomes seen in the Oregon cases, since about 22% of these patients had signet ring, poorly differentiated pathology and would not be expected to benefit from CRT.

Most patients having stage IB–III resected gastric cancer do benefit from CRT, and this therapy, as delivered in INT116, is considered a standard of care.<sup>2,3</sup> If this is the case, why did roughly 63% of eligible patients in Oregon not receive this treatment? Enestvedt et al point out that age was an important factor, with the median age of CRT patients being substantially younger than the median age of those not receiving CRT (64 vs. 75 years). It is of interest that the median age of patients selected for participation in INT116 was 62, perhaps representing a bias of investigators toward offering participation in the study to younger rather than older patients. It is indeed likely that older patients are likely to have a higher prevalence of comorbidities that would prevent or hinder tolerance to CRT. We have no data on the incidences of relevant comorbidities in the Oregon patients.

Age bias is common, and all thoughtful clinicians should question the ability of older patients with chronic conditions to

tolerate aggressive anticancer therapies. In general, patients of any age who have adequate major organ function and PS will tolerate therapy as well as younger patients with the same medical condition. Another common feeling is that older patients will not benefit from adjuvant therapy as much as younger patients do. Although this question has not been looked at in stomach cancer, it has been examined in colon cancer and the results showed that older patients benefit to the same degree as younger patients.<sup>7</sup>

Another important factor with regard to older patients and cancer treatment is the issue of “social or logistical ineligibility.”<sup>8</sup> This term refers to the needs of some older people for a social support network to provide transportation and general care provision, such as help in the home with activities of daily living. Patients requiring such support may encounter significant logistical problems initiating and completing a complex therapy regimen such as postoperative CRT and therefore they would be considered ineligible for such treatments.

Finally, other factors to consider in evaluating the relatively low rate of adoption of CRT in gastric cancer in Oregon are issues regarding the organization of cancer care delivery. Postoperative CRT in stomach cancer is a complex process requiring smoothly integrated multimodality care and coordinated decision making by surgeons, radiation oncologists, medical oncologists, oncology nurse specialists, and social workers. It is difficult to organize this type of patient management in a fragmented oncology care delivery environment. The multimodality care required is best delivered in a cancer center environment—in either a community or academic setting. It would be help-

ful to know in what sorts of care environments the patients in Oregon were managed. Were many patients in coordinated cancer care delivery programs? And was there a higher probability of receiving CRT if patients were seen in some sort of cancer center? Answers to such questions could render the results of the Oregon study more meaningful in relation to the post-INT116 clinical climate.

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## Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.