Adenocarcinoma of the pancreatic head: can survival be improved?

Adenocarcinomas of the pancreatic head have a dismal prognosis, with over 80% of patients having advanced disease at presentation, beyond the scope of curative therapy. Pancreatic resection by pancreatectoduodenectomy remains the treatment of choice when the tumor is resectable, as it provides benefit in 10%-20% of cases and five-year survival of 5%-24%. Results following resection are best when the tumor is small, the lymph nodes are uninvolved and the resection margins are clear.

There is little data on this subject emerging from the Indian subcontinent. In this issue, Wagle et al report the results of 45 patients with periampullary carcinoma, including 14 with pancreatic adenocarcinoma, who underwent resection. The overall mortality was 11%; the mortality rate among patients with pancreatic head carcinoma is not stated. There were no deaths following the last 23 resections.

During the last decade, the results of pancreaticoduodenectomy have improved steadily worldwide, with major morbidity rates of 20% and mortality rates fewer than 5%. Resection in localized cancer improves both survival and quality of life. In more advanced tumors, resection may improve survival but the quality of life remains poor. Increasing the radicality of the tumor resection by extended lymphadenectomy including clearance of retroperitoneal tissue posterior to the uncinate process has not improved survival.

How can we improve the outcome? A host of newer approaches – hormonal therapy, immunotherapy, radiopharmaceuticals, and novel chemotherapeutic agents – have failed to provide more than modest benefit.

Can radiation or chemotherapy improve survival? Radiation therapy can now be safely administered at high doses (50 to 55 Gray) without serious side effects. Newer chemotherapeutic agents such as gemcitabine and miloxantrone are also available. Although non-randomized reports have shown improved survival with postoperative chemoradiation, prospective studies have failed to produce significant benefit. Further, up to 20% could not be inducted into the regimen because of poor general status. Recently, Wanebo reported a 11% five-year survival rate among patients with locally advanced pancreatic head cancers who received neoadjuvant 5-fluorouracil and cis-platinum with 45-Gy external radiation followed by surgical resection. The nutritional status of patients was maintained during this period by enteral feeding through jejunostomy tubes. One patient in this group survived for 96 months.

Recently the attention has shifted to molecular approaches. Numerous genetic alterations in oncogenes and tumor suppressor genes have been observed; they include the p53, k-ras, p16, DPC-4, BRCA 2 and others. A tumor that expresses the p53 gene is less susceptible to radiotherapy and chemotherapy. On the other hand, the p16 gene is associated with better survival characteristics. There is thus an inverse ratio between the p53 and p16 genes. By enhancing p16 expression or by restoring the wild-type k-ras or p53 function, tumor growth can be arrested. Endoscopic ultrasound may play a important role in such manipulations.

Metalloproteinases are proteins that participate in basement membrane degradation. Combining these with chemotherapeutic drugs such as gemcitabine improved tumour control in experimental animals. Similarly, angiogenesis factors are also implicated in tumour growth and their inhibition would help in tumour control.

Gene therapy is attractive in concept, but for the present, the situation is grim. Surgical resection provides the best palliation in patients with good Karnofsky performance status. Adjuvant therapy by chemo-radiation may provide additional survival benefit, but care must be taken not to jeopardize quality of life. The dictum ‘curing wherever possible, but caring always’ may apply.

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References


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