

86

Advances in the treatment of cervical carcinoma: hemoglobin, hypoxia and concurrent chemo-radiotherapy

G. Thomas. University of Toronto, Radiation Oncology, Toronto, Canada

Since the National Cancer Institute of the U.S. issued a rare clinical announcement in February of 1999, the use of weekly cisplatin chemotherapy concurrently with radical irradiation has become the standard of care in the management of patients with advanced cervical cancer. Five randomized trials and a meta-analysis have shown an overall survival benefit of 10-15% for the combined strategy. However many controversies remain with respect to optimal therapy of advanced cervical cancer. To be discussed will be the lack of data explicitly supporting weekly cisplatin as the concurrent treatment of choice, the apparent relative lack of benefit for some stages and extents of disease e.g. stage IIIB, the magnitude of incremental value when chemotherapy is added to optimized radiation, or given when para-aortic nodes are involved, and the lack of impact on distant metastases rates. A large randomized Canadian trial revealed no benefit from the use of weekly cisplatin; one large randomized trial using mitomycin and oral 5FU without cisplatin has shown a survival benefit; single agent epirubicin given concurrently and as adjuvant has also shown a survival benefit with a reduction in distant metastases. Thus, questions remain: what is the optimal chemotherapy agent(s) and schedule? Does adding chemotherapy to optimal radiation improve the therapeutic ratio? Do only some sets of patients benefit from concurrent chemotherapy? Will adjuvant chemotherapy in addition reduce distant metastases?

Additional strategies to improve the treatment of cervical cancer are based on overcoming the recognized negative effect of tumor hypoxia on response to radiation and chemotherapy. Hypoxia causes radiation and chemotherapy resistance and also induces genes which lead to angiogenesis and the development of a more aggressive tumor, phenotype. Low hemoglobin levels during radiation therapy are also associated with inferior local control and survival in cervical cancer. A retrospective Canadian study of over 600 cervical cancer patients treated with definitive pelvic irradiation revealed on multivariate analysis that hemoglobin levels during radiation treatment were second only to stage for prognostic importance. Survival was 25% better if the average hemoglobin was greater than or equal to 120g/l regardless of whether the patient started with high or low hemoglobin and received transfusion. Pelvic relapse was halved, and distant metastasis rates were significantly lower in those with high hemoglobin. Confirmatory data, as yet unpublished from the Gynecological Oncology Group, confirmed the importance of hemoglobin levels during concurrent cisplatin radiation treatment in over 400 patients. Thus although the relationship between anemia and hypoxia is unclear, both correlate with survival levels. Understanding these relationships and underlying mechanisms allows the development of possible interventions in the "hypoxia-hemoglobin" pathways to improve outcomes. These will be discussed.

87

Chemotherapy and new approaches in cervical cancer

J.B. Vermorken. University Hospital Antwerp, Department of Oncology, Edegem, Belgium

The main players in the management of patients with CC have been and still are surgery and radiotherapy. The role of medical treatment, in the past merely used for palliation, has now become more promising when integrated in the primary treatment of the disease. It still can be concluded that there is no standard therapy for patients with recurrent/metastatic CC. Single agent cisplatin is a good option, but preferably such patients should participate in trials. With respect to the treatment of primary disease, neoadjuvant chemotherapy (NACT) followed by radiotherapy in patients with locally advanced disease cannot be recommended at the present time. The same is true for NACT followed by surgery, although some randomized trials suggest an improved outcome, in particular for patients with stage Ib2, IIa and IIb disease. Data on adjuvant chemotherapy are scanty and inconclusive. Chemoradiation is the new standard anno 2003 for patients, who otherwise would be treated with radiotherapy, based on several randomized trials and a meta-analysis. Novel strategies include the use of new drugs (taxanes, topo-I-inhibitors, vinca-alkaloids, gemcitabine), new combinations, dose dense therapies, the combined use of hyperthermia and chemotherapy, radiotherapy or both, the use of new cytotoxics or non-cytotoxics to enhance the effect of radiation therapy, methods to overcome hypoxia during radiotherapy and gene therapy.

References

- [1] Benedet JL, Odicino F, Maisonneuve P, et al. Carcinoma of the cervix uteri. In: Boyle P, La Vecchia C, Walter A (eds), Annual Report on the Results of Treatment in Gynaecological Cancer. J Epidemiol Biostat 2001; 6 (1): 5-44.
- [2] Vermorken JB, Eisenhauer EA. Current developments in the treatment of cervical cancer. CME J Gynecol Oncol 2001; 6 (1): 52-60.
- [3] Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systemic review and meta-analysis. Lancet 2001; 358: 781-6.

88

Quality control in surgical oncology: breast cancer

J. Geraghty. Tallaght Hospital, Department of Surgery, Dublin, Ireland

The delivery of a quality service is of fundamental importance in the care given to patients presenting with cancer. The demand for such quality is led both by the medical and allied professions. The medical profession and societies which govern it are increasingly preoccupied with standards of care and are moving steadily towards systems which allow measurement of such standards on an individual basis as well as defining standards of care for institutions. Surgery is the mainstay of treatment for most solid tumours and as such quality control in surgical oncology is of fundamental importance in optimising disease free interval and survival. Other treatment modalities such as chemotherapy or radiotherapy cannot compensate for inadequate surgery.

The development of the concept of a specialist breast unit has been the single most important advance in recent years and the evidence is now clear that such a structure enhances quality of decision making and quality of patient care and as such will eventually impact on disease free interval and survival. Such a structure recognises the fundamental principle in the management of breast cancer that a multi-disciplinary approach is preferable to that where decision making is governed by one discipline alone. The surgical oncologist is pivotal in this context, as he/she is invariably the first point of contact along the care pathway in the hospital setting. It is the responsibility of the surgeon to diagnose breast cancer, to ensure that there is a multi-disciplinary team approach to decision making and to then introduce the patient into this process.

The triple assessment or rapid diagnostic clinic is the recognised method of establishing a diagnosis in symptomatic breast cancer. It is clear that quality control in diagnosis is not just an issue of quality of the surgical oncologist but also relates to many other quality issues including quality of radiography, quality of reporting of imaging and perhaps most importantly quality in fine needle aspiration cytology.

The determination of nodal status is a crucial issue in quality control in surgical oncology as this is the single most important prognostic indicator on which adjuvant treatment is based. Inadequate staging due to poor quality surgery will impact on disease free interval and survival. The advent of sentinel node biopsy has compounded matters and whilst axillary clearance still remains the gold standard, it is at odds with the current thrust towards a minimalist approach in surgical oncology typified by the breast conserving approach.

In summary the surgical oncologist has a pivotal role in the management of breast cancer in both surgical intervention and as the first point of contact at the breast clinic which acts as the platform on which the patients path is determined. As such, quality of patient care is governed by the technical excellence of the surgeon and his/her ability to coordinate the multidisciplinary approach to the patient at both diagnostic and therapeutic levels.

89

Rectal cancer surgical quality – the key to effective multimodality treatment

C.J.H. van de Velde, K.C.M.J. Peeters. Leiden University Medical Center, Surgery, RC Leiden, The Netherlands

Rectal cancer poses a challenge to surgical, radiation and medical oncologists. One of the major problems in the treatment of rectal cancer has been the inability to achieve local control. Local failure is a serious problem which causes severe disabling symptoms that are difficult to treat and often kill the patient. In an attempt to improve local control and survival, many adjuvant treatment modalities have been investigated in the past. Results of studies that explored the role of radiotherapy showed that preoperative radiotherapy is more effective than postoperative radiotherapy in reducing