

WEDNESDAY 15 SEPTEMBER 1999

Symposia

1202

Screening for prostate cancer: Preliminary evidence from randomized studies and epidemiological data

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Prostate cancer can be diagnosed early with the aid of prostate-specific antigen (PSA) and digital rectal examination (DRE). This diagnostic algorithm applied to the general population will produce lead time in the range of 6–10 years. Demonstration projects and randomized studies have shown the feasibility of this approach. The question, however, whether life is prolonged by early detection and early treatment remains unanswered.

The "European Randomized Study of Screening for Prostate Cancer" (ERSPC) aims at showing or excluding a mortality reduction for those screened and treated with respect to those managed according to regional routines. More than 150,000 men have been recruited, the study runs in its fifth year. Preliminary data show a significant stage shift in the screened population with respect to controls and to historic controls. In the Rotterdam section the prevalence of metastatic disease is only 0.6% as opposed to about 25% in the cancer registry of neighbouring Amsterdam. Data relating to these intermediate endpoints will be presented. A final evaluation of the international study, in which centers in Finland, Sweden, The Netherlands, Belgium, Italy, Spain and Portugal participate, will only be known around the year of 2008.

1203

Is colorectal cancer screening worthwhile?

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Colorectal cancer screening has been widely researched over the past twenty years. Randomised trials of faecal occult blood testing (FOBT) published in the past half decade offer conclusive evidence of an effect on colorectal cancer mortality. Studies continue to examine the use of flexible endoscopy in population screening. Identification and colonoscopic surveillance of high risk families is widely accepted as an effective exercise.

FOBT applied biennially decreased mortality by around 20% in the three trials reported recently. Shortcomings include poor sensitivity and specificity (50% of cancers missed, 90% of positive tests not due to cancer), and low compliance. Immunological detection of human haemoglobin, and stool tests for gene mutations are not yet useable alternatives. Colonoscopy as the subsequent diagnostic test after a positive FOBT carries significant risks if not delivered as a high quality service.

Once-only flexible sigmoidoscopy (FS) around age 60 may be a realistic alternative; the UK multicentre RCT involving 400,000 people has recently finished recruiting patients; incidence and mortality data will not be available for several years. Unlike FOBT, FS is likely to have a substantial effect on incidence as well as mortality.

In high risk families, interventions using colonoscopic polypectomy and prophylactic surgery substantially diminish cancer risk. At-risk families may be difficult to identify and hence to offer appropriate screening programmes. Molecular identification will become important in the future.

1204

How do we know that breast cancer screening is effective?

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There is an international agreement that breast cancer screening is effective, and several health ministries have taken a decision to implement screening in their health care activities. The understanding of the effectiveness of screening is based on knowledge about natural history of breast cancer, where detection in an early phase of the disease is correlated to better survival. Furthermore, there exists a method to detect breast cancer

in an early stage, i.e., mammography. Randomised trials have also shown a decreased mortality on approximately 30% in screened groups in comparison to control groups. Methods for evaluating the effect, but also for controlling the quality of a routine screening programme in a service setting, are mainly indirect and dependent on surrogate measures. Such measures are e.g., participation rate, recall rate, positive predictive value of biopsy, cancer detection rate, rate of small cancers and cancer in situ, and rate of interval cancers. The effect on breast cancer mortality by population based routine screening is related to the quality of the radiological examination. The effect is also related to the participation rate (or coverage of target population in a decentralised setting) and to the quality of further assessment and treatment of women with abnormal findings. To date, there are no recommended epidemiological methods on how to evaluate a routine screening programme in terms of mortality reduction. Estimation of the impact of screening on mortality could be made by comparing mortality rates in the screened population with e.g., data from a reference period (historical data), rates in a reference population, expected and prognosticated mortality, excess mortality, or time trends. Different papers focusing on the evaluation of the effect of routine screening in a service setting as well as epidemiological and methodological problems will be discussed.

1205

Cervical cancer: New approaches and mass screening

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Depending on the technology used, the automation in cervical cytology in US is supposed to improve the sensitivity of Pap-testing between 11% and 15%; by consequence life expectancy increase by 5 hours to 1.6 days per woman screened and the cost per year of life saved rose from \$7777 with quadriennial screening to 166,000 with annual screening.

The greatest obstacle to cervical cancer prevention remains the failure to be tested, not the testing methodology. These technological improvements can be used as a part of less frequent screening but if their cost discourages the participation in screening programmes, their will not reduce the occurrence of invasive cervical cancer.

Strategies aimed at increasing the number of women screened, particularly among those who have not had a Pap smear, are likely to be much cost effective than computer-assisted rescreening at reducing cervical cancer morbidity and mortality.

HPV testing potentially may be very useful for primary screening or secondary triage of patients with certain lesions. Data on the effectiveness of these approaches as well as clear cost benefit analysis are expected from several large trials.

Antibodies against Cd6 and Mcm5 stain abnormal cells in cervical smears with high sensitivity and specificity raising the possibility of automating the cervical screening test.

Questions concerning dosage, adjuvants, boosters of a vaccination programmes, targeting HPV 16, 18, 31, 45 are under consideration.

Vaccination of adolescents has been suggested for preventing HPV infection. The eventual introduction of HPV vaccination may vary risk profiles in women of different ages: some decades would be needed before eradicating

1206

Multidisciplinary approaches in head and neck cancer – Where do we go from here?

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For a long time, either radical surgery, S, (most often with postop irradiation, XRT) or definitive XRT, (with S in reserve for salvage) were the two preferred treatments for advanced but resectable larynx and hypopharynx SCC. No randomised trial has compared both approaches. The appearance of active chemotherapy, CT, and the frequent correlation between CT and XRT

sensitivities reopened the discussion with a new strategy: induction CT followed, in good responders, by XRT or, in poor responders, by S. To date, 3 randomised trials have been published with such a design. The VA trial on larynx and the EORTC 24891, for hypopharynx had similar conclusions. In both trials there was no difference in survival between this experimental approach and the standard treatment (S + postop XRT) but 50% to 66% of survivors could retain their larynx. In the French trial (GETTEC) only T3 larynx SCC were eligible. The survival was poorer in the experimental arm. A meta-analysis (MACH-NC) of the 3 trials concluded in a non significant trend for a better survival in the surgical arm but 58% of larynx could be preserved in the experimental arm.

Conversely, subtotal surgery may avoid performing, in selective cases, a total laryngectomy. Finally, notable advances have improved XRT results: new fractionation, acceleration, both or concurrent administration of XRT and CT.

Clearly, there are different ways to preserve the larynx function which are still to be compared. As a result, this approach still remains in the field of clinical research.

1207

Chemoradiotherapy as treatment of choice in oesophageal cancer

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In a prospective randomized controlled trial of neoadjuvant chemoradiotherapy versus surgery alone for patients with Carcinoma of the oesophagus we have observed that multimodal therapy can downstage tumour size, node stage, lymphovascular invasion and radial margin involvement. A complete response was obtained in 25% of adenocarcinomas and 32% of squamous carcinomas.¹

Surgery may not have been necessary in some of these patients. One patient who did not proceed to surgery because of a severe myocardial infarct was tumour free for 4 yrs before developing a recurrence. Of 2 patients in whom surgery were omitted because of deteriorating performance status, 1 survived 2½ yrs before developing a recurrence and 1 was tumour free at last review at 2 yrs. One patient survived 30 mths despite having an incomplete response. Nine further patients survived for short periods or are still being followed up.

[1] Walsh T., Noonan N., Hollywood D., Kelly A., Keeling N., Hennessy T., A comparison of multimodal therapy & surgery for esophageal adenocarcinoma. N. Eng. J. Med. 1996, 335/462-7.

1208

Chemo-radiotherapy reduces the need for a permanent colostomy

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A permanent stoma can rarely be avoided during radical surgery for squamous carcinoma (SCC) of the anus or for adenocarcinomas (adenas) of lower third of the rectum. Since primary radiotherapy (XRT) yields colostomy-free survival rates of 60-80% for SCC, it should be considered primary treatment, with surgery for failures. However, for adenos the cure rate is below 50% for tumours over 5 cms diameter. After XRT for adenos, planned local excision is safe but for tumours >5 cms radical surgery with pouch procedures are preferred. Concomitant cytotoxic chemotherapy (chemo) appears to enhance the XRT-sensitivity of both tumours. In SCC three large phase III clinical trials have been demonstrated an improvement in local control when XRT is combined with 5-fluoracil (5-FU) with no major increase in toxicity. Similar improvements appear in non-randomised studies in adenos, but randomised studies have shown increased postoperative complications following chemo-XRT. Since the optimal chemo-XRT schedule has yet to be decided, phase I/II studies should be conducted on patients with advanced inoperable/recurrent adenos using drugs with known activity like raltitrexed, oxaliplatin or irinotecan.

1209

Multimodality approaches in breast cancer: What have we learned?

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There is now an increasing need for a multidisciplinary approach to the treatment of early breast cancer to obtain a high local control rate and

survival. With this multidisciplinary approach, there is a high probability of preserving the breast.

An increasing number of patients with DCIS are being discovered due to screening programs. The preliminary results of clinical trials in DCIS demonstrate that radiotherapy can reduce the local excision after microscopically complete excision of tumors up to 5 cm. On the other hand, a longer follow up is still necessary to define which subgroup will benefit most from radiotherapy.

For stage I and II invasive breast cancer, breast conserving therapy (BCT) has been shown to result in equivalent survival rates to mastectomy. With the introduction of the sentinel node biopsy, the treatment morbidity is reduced considerably for a large number of patients. Patients younger than 35 years old have a higher locoregional recurrence rate after breast conserving therapy. The increased use of adjuvant chemotherapy has reduced the amount of local recurrences; it is uncertain what the contribution is to the results of BCT in younger patients.

The difference in treatment outcome, which varies per institute, has led to an intensive quality assurance program. This has proved most effective as the results of a major EORTC trial (>5500 patients) showed much less variation in locoregional recurrence rate between participating institutes.

1210

Limb salvage for soft tissue sarcoma: Multimodal procedures or improved surgery?

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It is common observation that amputations for soft tissue sarcoma (STS) progressively decreased in the recent decades. In the same span of time different multimodal treatment policies were experienced to improve local and systemic control with an impact on survival: perioperative radiation therapy, adjuvant chemotherapy, isolated limb perfusion, and combinations. These adjuvant procedures are usually conceived to be responsible for improving limb salvage surgery, but their role was never proved. In the last 20 years the survival rate of patients with STS had a minimal improvement, if compared with the number of amputations which significantly dropped from 40/50% to 10/20%. We reviewed 1319 patients with extremity STS operated in our Institute in the period 1965-1998. The amputation rate stratified by years was respectively: 1965-, 75 = 71% (37/52 pts), 1976-CE85 = 16% (46/287), 1986-CE95 = 8% (61/764), 1996-CE98 = 3% (6/216). By their own any single procedure helped local control and conservative operations but in details: RT is the main adjuvant tool for local control, but its rationale, even if more standardized in the recent period, did not change grossly by years. Moreover the indication to RT, as for adjuvant CT, is usually decided postoperatively and has no role on the surgical choice between conservative versus ablative operation. Preoperative CT was employed in 143 cases (111 with intra-arterial delivery of Adriamycin): shrinkage of the lesion was documented in about 40% of cases, but the split from amputation versus conservative operation was estimated around 4%. More recently hyperthermic isolated limb perfusion chemotherapy seems to improve these conservative possibilities: we perfused 70 cases, mainly in the last five years and their final role in local control is still under evaluation, however not responsible of the important improvement reported between the CE70ties and the CE80ties. Surgical reconstructive methodologies and vascular prosthesis were employed in less than 10% (128/1319) of our operations and changed the surgical indication in favour of limb sparing surgery in less than 3%. In conclusion all adjuvant or sophisticated procedures are effective on local control but do not give reason for the dramatic drop of amputations that is mainly due to improved anatomo-surgical knowledge and practice.

1211

Combination therapy for osteosarcoma

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Osteosarcoma, the most common primary bone cancer, usually afflicts adolescents and young adults. The primary is often located in an extremity, and micrometastases to lung or bone are almost ubiquitously present. In order to be successful, treatment must eradicate both the primary and all metastases. Today, this goal can frequently be achieved by combining surgery with systemic chemotherapy. The main aim of chemotherapy in this setting is the eradication of micrometastases. Most successful protocols include two to four of the drugs methotrexate, doxorubicin, cisplatin, and ifosfamide.