trials of local treatments in early breast cancer beginning before 1995. Information was available for 78 randomized trials involving 42,000 women (23,500 in trials of radiotherapy (RT) vs. no RT; 9,300 in trials of more vs. less surgery; and 9,300 women in 17 trials of more surgery vs. RT).
Major findings from the update were: (1) breast cancer mortality was reduced with RT following breast-conserving surgery [hazard ratio 0.83, 95% CI 0.75−0.91 (p = 0.0002)]. This effect was seen for node-negative and node-positive disease and paralleled the substantial reduction in local recurrence seen at 5 years; (2) a reduction in breast cancer mortality was also seen post-mastectomy in node positive patients (p = 0.002). No effect was seen for node-negative disease; (3) an important relationship between local control and the impact on breast cancer mortality was observed. In most trials of RT, the impact on local recurrence was seen rapidly and substantially by 5 years. Little effect in breast cancer mortality was observed in the first 2−3 years, but a definite effect was seen at 10 years and was maximally at 15 years. Among the 25,000 women in whom there was a reduction in local recurrence at 5 years of >10%, there was an absolute reduction in breast cancer mortality at 15 years of approximately 5%; and (4) the use of radiotherapy was associated with an increased incidence of contralateral breast cancer (rate ratio (RR) = 1.18, p = 0.002), lung cancer (RR = 1.61, p = 0.0007), leukemia and soft tissue sarcoma. There was an associated increase in non-breast cancer deaths mainly involving heart disease (RR = 1.25, p = 0.00003).
Since this update the 2005/06 cycle of the EBCTCG has commenced including additional trials started in 1995–2000 with extended follow-up up to 2005. A preview of these findings and implications for clinical practice and research will be presented.

189 INVITED

Does everyone need breast radiotherapy?

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The risk of local tumour relapse has fallen to such low levels for most patients after breast conservation surgery, systemic therapies and radiotherapy for early breast cancer that it prompts reassessment of guidelines that recommend breast radiotherapy in all cases. Trials randomising to radiotherapy versus no radiotherapy primarily test treatment effect, but they also offer valuable prospective data on the consequences of observation (no radiotherapy) in well-characterised populations. These typically include women aged over 50 years with completely excised oestrogen receptor (ER) positive, node negative tumours less than 20 mm in microscopic diameter. Recent results have been interpreted as evidence that radiotherapy can be safely withheld in defined subgroups, but these judgements seem premature based, as they are, on trials with less than 5−10 years follow up. Nevertheless, several factors are likely to be driving local relapse risk down independent of radiotherapy, including patient selection for breast conservation and more careful attention to surgical excision margins. In addition, advances in adjuvant systemic therapy are having a significant impact. The 2005 update of adjuvant systemic therapy by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) confirms that 5 years tamoxifen or several months of polychemotherapy reduce the annual hazards of local relapse to a similar extent as distant metastases. This amounts to a 50% reduction in local relapse risk after 5 years tamoxifen in ER positive tumours. After cytotoxic therapy, the magnitude of local effect depends on drug regimen and ER status, but is substantial in ER negative tumours. Preliminary data from trials testing adjuvant aromatase inhibitors report a reduction in local relapse risk of around 30% compared to tamoxifen alone. The combined effects of tamoxifen and aromatase inhibitor are, therefore, comparable to the benefits of radiation (hazard ratio = 0.3). The effects of trastuzumab in patients over-expressing the HER2 protein are also impressive, reducing local relapse risk by around 50%. In conclusion, while it is not currently possible to confidently identify subgroups with <10% risk of local relapse at 10 years after surgery and appropriate systemic therapies alone, it is likely that selective avoidance of breast radiotherapy in defined subgroups will be possible in the next 5 years or so. The selection process is likely to take account of encouraging evidence that biological markers help to reliably define low risk subgroups.

190 INVITED

Partial breast irradiation – a valid option?

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Partial breast irradiation (PBI) is a new modality of radiotherapy, delivering radiation solely to the surgical area of excision in the setting of breast conservation of small breast cancer.
PBI was originally designed to allow breast conservation to patients with small tumors, who, because whole-breast radiotherapy (WBR) over several weeks could not be carried out in some areas due to distance to radiotherapy centers, costs, or long waiting lists, were treated with mastectomy. The first reports of PBI were of series of highly selected patients treated with conventional low-dose rate brachytherapy using Iridium 192, implanted through plastic catheters in the surgical site area, treating a wide volume, with doses around 50 Gy over 5 to 6 days. Reports from these experiences suggested that 5-year local control rates were similar to those obtained with WBR.
More recently, new techniques were introduced and are still under evaluation, aiming at targetting smaller treatment volumes, and at reducing the treatment time with accelerated irradiation (APBI). These techniques include: high dose rate brachytherapy, delivered through ambulatory care, or external beam photon radiotherapy. In both instances, a 50 Gy or more "biologically equivalent" dose is usually delivered in 10 or more fractions, twice daily with at least 6 hours interval, over 5 days. Another technique uses intraoperative radiotherapy with low-energy photons or electrons, delivering a single dose of radiation in the surgical bed immediately follwing excision. Results from these various techniques are reported with short follow-up in selected patients. Several prospective phase III randomised trials are ongoing in North America and Europe.
Obvious advantages of these techniques are practical: the reduction of overall treatment time makes it possible for patients to undergo treatments which otherwise they would be able to afford daily over several weeks, because of physical incapacity, distance to radiotherapy centers, professionnal constraints, or in some countries, cost of treatment. Treating the site of excision only with a predetermined margin would limit irradiation of organs at risk, such as the heart, lungs, or contralateral breast. Finally, the short overall treatment time would allow an earlier delivery of irradiation in patients who receive adjuvant chemotherapy.
However, this new technique raises many issues that need to be solved before it can be recommended for routine practice. Among them are the following:

- What will be the consequences of not treating the whole-breast, as achieved by mastectomy or WBR, as has always been the basis of the locoregional treatment of breast cancer? The rationale of this new paradigm relied on the observation that the majority of breast recurreces occurred within the area of the primary tumor location in the breast, which led to the postulate that only these recurrences shoud be prevented, wheras recurrences elsewhere in the breast would represent new primaries. However, some data suggest that, in the long term, WBR can prevent the occurrence of such elsewhere recurrences, the exact nature of which remain to be precisely determined by biological characterization.
- The planned treatment volume defined in most PBI techniques, usually encompasses the vague definition of the surgical cavity with arbitrary margins aimed at treating the microscopic residual disease and taking into account set-up variations and patient's respiratory movement. These definitions vary from one technique to another and are often mostly determined by the constraints of the technique itself. Therefore, the definition of margin in these techniques is highly imprecise.
- Hypofractionation has not been validated in the long term, using these particular regimen. Single doses, or high doses per fraction, with a short repair interval, may lead to increase long-term sequelae in the treated area; models of biological equivalence are not fully reliable, and need to be validated in breast cancer. Recent results from large, randomised multicentric studies of hypofractionated WBR suggest that regimen using 13 to 16 fractions can be safely applied, which are not much different from the 10 or more fractions used in the APBI regimen.

Finally, the technical delivery of whole-breast radiotherapy has dramatically improved in the recent years, allowing in most instances to safely prevent the unnecessary irradiation of organs at risk.
In conclusion, the concept of partial breast irradiation represents a significant shift in the current paradigm of breast-conserving treatment. It raises many unsolved issues that need to be validated in prospective trials, and its effects will have to be measured in the long term. It is much too early yet to determine whether it would be a becomme a valid alternative to whole-breast irradiation in selected groups of patients.

191 INVITED

The effects and interaction by multimodal therapies, radiation, cytostatics and trastuzumab, on cardiac toxicity

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Background: Postoperative radiotherapy reduces the risk for local recurrence with around 2/3. Adjuvant tamoxifen, cytostatics, and combinations with trastuzumab improve overall survival. For many patients, the use of systemic adjuvant therapies have presently to be combined with postoperative radiotherapy in order to obtain the most optimal results, trading of benefits versus increased side-effects.

Materials and Methods: Only a single prospective and randomized study has prospectively investigated when postoperative radiotherapy is to be integrated in relation to chemotherapy. Multiple studies have tested the effects by adding endocrine therapies to chemotherapy, and the addition of trastuzumab (T) to different chemotherapy regimens. When and how to integrate these modalities in relation to radiation will be discussed.
Results: Long term follow-up reveals increased cardiovascular toxicities by radiotherapy, although these side-effects have in the overview process been described to diminish in later studies.
The initial pooled analysis of the adjuvant US trastuzumab studies (NSABP B-31/NCCTG N9831), containing doxorubicin, cyclophosphamide (AC) and paclitaxel (P), revealed in an indirect comparison with the HERA study a "better" disease-free survival. In the US studies T was partly delivered concurrently with adjuvant P, while in the HERA study all T was given after the completion of chemotherapy and radiotherapy. The US studies, with AC, concurrent P and T, followed by radiotherapy and remaining T, revealed a likely higher risk of severe congestive heart failure (CHF) and systolic dysfunction, respectively; 0.6% in HERA compared with 2.5−3.6% CHF. Systolic dysfunction was 3.0% in the HERA study, while the concurrent strategies revealed 14−17%. In the third large US study BCIRG 006, the arm with concurrent T with docetaxel (D) and carbopaltin revealed a 0.4% risk of severe CHF, systolic dysfunction was reported in 8.6% of the patients. For the FINHER study with only nine weeks of T concurrent with D or vinorelbin at start of therapy the corresponding values were 0% and 3.5%, respectively.
Conclusion: For most patients, the likely best strategy is to deliver chemotherapy first, followed by radiotherapy and endocrine therapy. For those patients with HER2/neu positive cancers there is a potentially better effect by giving trastuzumab concurrently with taxanes, although the cardiac side-effects seem to be higher by this strategy, so the optimal strategy is so far not known.

Symposium (Thu, 27 Sep, 09:00−11:00)
Quality improvement strategies in cancer

192 INVITED

A mixed Dutch approach in the European perspective

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Being examples of performance The Netherlands did well in European comparisons of participation in EORTC studies of cancer treatment, of the presence of effective mass screening programmes (for cervical and breast cancer) and active participation in studies of screening for lung and prostate cancer; generally, it exhibited reasonably good results within the Eurocare studies, covering the diagnostic periods 1978−85, 1985−89, 1990−94 and 1995–2002, respectively with increasing populations covered, as well as in various high resolution care pattern studies of breast, colorectal, testis and prostate cancer. Although, and a bit later than desired, a huge government stimulated investment effort in radiotherapy equipment and manpower took place since 2001, there was great anxiety on the needed capacity and efficiency of the health sector, partly evoked by 'silent' demographic changes and permanent uncertainties on income of and power over doctors, who also became scarce due to inadequate deliberate ministerial policies to keep the number of medical students low since the mid 1980s; but they were doubling again since 2000 and training opportunities have enlarged in the meantime.
Since 2000 there have been several, seemingly uncoordinated but necessarily related, initiatives to come to a national cancer plan. On the one hand several explorative reports on the future of cancer prevention and cancer care have been published under the auspices of the Dutch Cancer Society, the major player in the domain of cancer research by fund raising and patient education: 3 reports on prevention (summarizing the evidence) by prudent exposure to UV (2002), diet (2004), physical exercise (2005), a report on colorectal cancer screening preaching diversity (2004), a report on the bright future of imaging (2005), a report on molecular diagnostics (2007) and biobanking, a report on waiting times (2006); they were also supported by an extensive report on trends in prevalence (incidence and survival) during the period 1990–2015 (2004). This latter report still provokes discussion on how to adress the rising demand for care (the number of cancer patients alive rising from about 500,000 in 2005 to 800,000 in 2015), especially in the domain of breast and colorectal cancer, skin cancer and related to older patients, for whom special care programs are needed that also adress co-morbidity, especially for the rapidly rising numbers of patients with cancer and diabetes. The aim of all these scenario-type of reports have been to stimulate the various players to take their responsabilities in terms of training, regionalization (here supported by the 9 Comprehensive Care Centres – CCC's – responsible for the promotion of quality of care at regional level), delegation of tasks to nurse-practioners and in fact promoting early diagnosis and also reluctance with cancer screening with its modest benefits and large resource & care implications.
Simultaneousy, In the period 2003−06 a major political change gave the health insurance companies responsability for buying health services, also competing on price and quality (as always difficult to measure etc), for which the Ministry of Health and new independent supervising bodies are trying to create optimal conditions, e.g. by promoting incentives for such competition, efficiency, patient safety ans also the introduction of electronic patient records. But also efforts to heva new (expensive) cancer drugs sooner available. Although aimed at greater efficiency, more restricting rules and controls are also resulting and care providers like GP's suffer. The results are mixed for the various specialists whose numbers are increasing rapidly.
A substantial, rather heavy, effort to write a national plan was also undertaken by the major players (the Dutch Cancer Society, the 'united' CCC's, Insurance companies, cancer patient societies and the Ministry of Health). A large report arrived in 2004, but was not received with much enthousiasm, because it lacked a perspective (except for wider application of psychosocial care) especially with respect to research and development and in fact there had been little professional involvement. Recently, some efforts take place in reviving, but in fact many professionals are making hteir own plans in accordance with the new regime of governance by insurance companies.
The importance of professional involvement can be underscored by many examples, the best (in my opinion) being the impressive improvements in rectal surgery and preoperative irradiation which have taken place in the last 15−20 years; they are currently followed in the domain of colon cancer management and many other initiatives at regionalization of surgical oncological care.
Conclusion: through a diversity of professional initiatives cancer care is definitely improving in the Netherlands. The best policy is to support this.

193 INVITED

The UK programme

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Abstract not received.

194 INVITED

The French approach – The French Cancer Plan and its instrument the French National Cancer Institute (INCa): A centre of hope in the fight against cancer

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Fighting cancer in the world, and particularly in France, means more than just taking up a public health challenge. Among the 10 million new cases and 6 million deaths worldwide in 2000, France accounted for 280,000 new cases and 150,000 deaths. By 2020, it could kill 10 million people worldwide every year.
Beyond the disease strictly speaking, cancer leads to a number of social inequalities, ranging from exclusion and discrimination to psychological problems. With the ultimate goal of cure, science plays a key role in the fight against cancer, basing its research both on simple mechanistic paradigms of cancer and more complex process-based ones. Considering the huge increase in medical needs – as regards the epidemiology and chronicity – and the cost and complexity of the new treatments, the next step consists in transferring relevant information and updated knowledge from the laboratory to the bedside (through translational research and valorisation), thus adhering to the objective of putting patients at the heart of cancer care – both in access and quality.
The landscape for cancer in France reflects the challenges of the disease. Although the country has the best survival rate after cancer in Europe, the number of cases doubled between 1980 and 2000. In addition, a lack of public health policy is evident in a country where there is the highest premature mortality in men. The principle of universal and unlimited access to care in France results in 3 million mammograms, 1.5 million colonoscopies and 6 million Pap tests administered every year, undermined by a lack of organization and cost-efficiency.
The French healthcare landscape shows geographical discrepancies as well as a lack of equipment and of respect to patients, despite a high level of access to modern medicine. In 2002, France had 10.3 scanners per million inhabitants, 3.8 MRIs and 0.2 PET scans with waiting times of 41 days for a scanner and 39 days for an MRI. There is also an increase in the demand for health services with, for example, a 12% per year increased demand for chemotherapy. French cancer patients have insufficient access to non-medical care (including rehabilitation and counselling) and ambulatory care (despite a significant progress made in the palliative care and pain management areas.)