

Concerning the interpretation of QL scores, it is not yet clear how to understand a given difference or change in scores. Is a statistically significant improvement of 7 points in 'emotional functioning' important to patients? A number of different approaches are being explored to better understand the importance of different magnitudes of change. One of these is the Subjective Significance Questionnaire, developed by Osoba as a means of better understanding changes measured by the EORTC QLQ-C30 QL questionnaire. Other approaches use wellknown clinical 'events' (e.g. the impact of a given treatment) as 'anchors': the effect of the wellknown treatment on QL scores can then be compared to the impact of a new treatment.

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Update on BRCA1 and BRCA2: Molecular biology and genetics

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Women with an inherited alteration in one copy of BRCA1 or BRCA2 are at very high risk of developing breast cancer. Recent data suggest that BRCA1 plays a critical role in the cellular response to DNA damage. This may occur by BRCA1 participating in signals to stop cell cycling so that repair can take place, or to induce cell death if the damage is too great to be repaired. The end result of cell replication in the presence of damaged DNA is malignant transformation, thus these insights offer an explanation of the role of BRCA1 in preventing cancer.

We have identified a link between BRCA1 and three other important proteins – the cell cycle inhibitor p21, the tumor suppressor/DNA repair gene p53 and the regulator of cell death gene Bax. We have shown that BRCA1 plays a role in modulating the ability of p53 to induce these genes, possibly serving as a cellular switch after DNA damage. In addition, we have completed studies of the kinetics of BRCA1 regulation in response to DNA damaging agents, further supporting the role of BRCA1 as a sensor of damage that then functions as a switch after damage occurs. As BRCA2 interacts with BRCA1, it is likely that both genes function in a similar pathway.

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Genetic heterogeneity of hereditary breast cancer

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Between 6 and 19% of women with breast cancer have at least one affected relative at the time of diagnosis, but not all of them are expected to be true genetic cases. Families with inherited breast cancer are characterized by multiple early-onset and/or bilateral cases, and frequent occurrence of specific other malignancies (notably ovarian cancer). The most likely model explaining the observed familial clustering is one incorporating the transmission of an autosomal dominant susceptibility locus. Yet the observed risk to siblings can be equally well explained by either an infrequent high-risk gene, or a low-risk gene with high population frequency. In fact, it is now clear that inherited breast cancer is determined by a number of genes conferring a range of penetrances. Rare high-risk genes are most amenable for detection by linkage analysis, and this has led to the discovery of BRCA1 and BRCA2. They jointly explain the large majority of families with either the breast-ovarian cancer syndrome, with at least one case of male breast cancer, or with at least 6 cases of breast cancer diagnosed under 60. However, roughly 60% of the families with 4 or 5 cases of breast cancer diagnosed under 60, and no cases of ovarian cancer, are not accounted for by these genes. Other genes, such as PTEN and TP53, cause primarily specific cancer syndromes, of which breast cancer forms just one constituent. Hence more breast cancer susceptibility genes remain to be identified, which are probably of lower penetrance than BRCA1 and BRCA2, although they still predispose to breast cancer at a young age.

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Clinical management of the BRCA heterozygote

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Significant progress has been made in defining the genetic epidemiology of hereditary breast cancer, but the clinical approach to individuals with an inherited predisposition continues to evolve. Different questions arise

for women who are already affected with breast cancer and for those who have not yet developed the disease. In approaching the affected heterozygote, the central clinical question is whether cancer arising in the setting of a germline mutation requires a different clinical approach from that arising without such a predisposition. BRCA1-associated breast cancers are usually rapidly proliferating, aneuploid, infiltrating ductal carcinomas of high histologic grade, lacking hormone receptors, with a relatively high frequency of somatic p53 mutations. HER2 overexpression appears to be uncommon. Although there are fewer data, BRCA2-associated cancers may have a histologic appearance and immuno-phenotypic profile more closely resembling "sporadic" cancer. Early studies suggested that the prognosis of BRCA-associated cancer was similar to that of sporadic cancers, but recent unselected series suggest that outcomes are actually worse, as would be expected from the prognostic factor profile.

In approaching the unaffected heterozygote, the major issue is the relative effectiveness of screening strategies compared to primary prevention approaches with surgery or chemoprevention. Current guidelines are based on expert opinion alone. The level of cancer risk in this population justifies aggressive screening, but the effectiveness of mammography and ovarian cancer screening remains undefined. Risk-reducing surgery appears to be effective, but failures do occur and the acceptance of procedures varies. Studies of new screening and prevention methods are underway.

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Prophylactic interventions – Effective, harmful or of unproven benefit?

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Most knowledge relating to the genetic basis of cancer and particularly inherited cancer predisposition has only recently been discovered. Inevitably there is major interest in risk assessment, genetic testing and strategies which may be used to reduce morbidity and mortality among those who carry mutations conferring inherited cancer risk. A futuristic vision of cancer care takes us towards a circumstance where advanced disease is no longer seen. Instead we can focus on detection of high-risk individuals and employ effective screening strategies, chemoprevention or prophylactic surgery to reduce or eliminate risk of cancer death. Unfortunately life is not so simple and care must be taken to inform patients and others presenting for genetic testing of the limitations and complexity of issues surrounding hereditary cancer predisposition. Each site presents specific issues with regard to screening, chemoprevention and surgery. For HNPCC carriers, for instance, screening through colonoscopy can improve survival for at-risk individuals but screening of female carriers for extracolonic malignancy is of unproven benefit. There is no evidence for the use of chemoprevention and prophylactic colectomy, while an option for some, is also of unproven benefit. Issues such as this are similarly complex for breast and ovarian cancer. The major beneficiaries at present from genetic testing are those who have a negative test where a known, disease-related mutation exists within a family. Noncarriers can be released from the anxieties which prevail and do not need the increased surveillance now recommended for those carrying mutations or those with a high risk based on family history data. Information regarding prophylactic interventions is steadily accumulating but, as yet, efficacy remains limited for many strategies, potential for harm exists and much proof remains to be gathered.

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Role of chemotherapy (CT) in non metastatic head and neck squamous cell carcinoma (HNSCC): Results of an international meta-analysis

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Purpose: In 1994 an International Collaborative Group (MACH-NC) was set up to perform a meta-analysis of randomized trials in order to evaluate the role of CT on survival of patients with HNSCC.

Methods: 10 741 patients (pts) randomized between 1965 and 1993 in 63 trials comparing loco-regional treatment to same treatment plus CT were included. Nasopharynx and "organ preservation" trials were excluded. Collection of individual patient data, updated for 2/3 of the trials, allowed extensive checking. Logrank test stratified by trial was used.

Results: A small (4% at 5 years), but significant ($p < 0.0001$) survival benefit in favor of CT was shown. However the observed benefit was dependent upon the type of CT used ($p = 0.005$): no significant benefit for adjuvant CT (benefit 1%, 8 trials*, 1 854 pts*) as well as neoadjuvant CT

(benefit 2%, 31 trials*, 5 269 pts*) whereas the absolute benefit at 5 years was 8% for **concomitant CT** (26 trials*, 3 727 pts*). Exclusion of small trials (<80 pts) or old trials (<1980) did not modified the results. The effect of CT was not significantly different according to the tumor stage and the tumor site (larynx, hypopharynx, oropharynx, oral cavity).

Conclusion: CT led to a small but significant improvement in survival. The observed benefit depended on CT timing and was the highest with CT concomitant to radiotherapy.

*2 trials with 3-arms: 1 neoadjuvant CT, 1 concomitant CT & 1 control
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Is there still a place for chemotherapy in patients with locally advanced head & neck squamous cell carcinoma?

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Combination chemotherapy such as cisplatin-5-fluorouracil is effective in inducing a high rate of tumor responses in patients (pts) with advanced Head & Neck (H&N) cancer. In the recent decades, chemotherapy was included in organ preservation strategies or in combination with radiotherapy to improve the local control in pts with non-resectable diseases. Chemotherapy was also proposed in neoadjuvant and adjuvant settings with the aim of reducing the risk of distant metastases and improving survival. Recent results of an individual-patient based meta-analysis including about 11,000 pts and 63 controlled-trials (from 1965 to 1993) were striking. This study showed a small but significant overall reduction of the risk of death of $10 \pm 2\%$ translating in an absolute survival benefit of only 4% at 5 years in pts receiving chemotherapy ($p < 0.0001$). The benefit was observed when chemotherapy was concomitantly associated with radiotherapy (reduction of risk of death $19 \pm 3\%$, absolute benefit at 5-year 8%). Conversely, no benefit was observed in pts receiving chemotherapy for larynx preservation or treated in adjuvant settings. Overall, neoadjuvant chemotherapy did not significantly improve survival in pts with H&N cancer. However, a trend toward an increase of survival was observed in patients receiving cisplatin-5-fluorouracil regimens. Preliminary results focused mainly on survival. More data generated from this meta-analysis on disease free survival, occurrence of second primary, and non-cancer related deaths (due to concomitant tobacco related diseases) will be required before drawing a definitive conclusion on the impact of chemotherapy in H&N cancer. However, this meta-analysis emphasizes the small benefit of current routine chemotherapies on the outcome of pts and encourage prospective clinical trials with original drugs and strategies. This shows that more effective anticancer agents are urgently warranted to improve the outcome of patients with H&N cancer. From those investigational agents we will discuss recent data obtained with taxanes, antifolate analogues, and recent biological programs targeting selectively p53 in H&N cancer cells.

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Radiotherapy in head and neck cancer

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The management of Head and Neck carcinomas is nowadays based on multi-disciplinary approaches, especially in patients with bulky tumors. Their configuration varies according to host- and tumor-related factors and are aimed at improving both cure rates and quality of life. Radiation therapy constitutes one of the pillars of this therapeutic management, both for early and locally advanced disease.

In patients with *early disease*, radiotherapy is indeed as safe as surgery as regards local control and survival rates and, as a conservative treatment, it also offers a quality of life surgery is not always able to offer, especially when radical procedures can not be avoided. The role of new techniques of high conformality radiotherapy and brachytherapy is probably determinant to reduce the incidence of severe late toxicity and offer major opportunities of radiotherapy treatments in patients with second malignancies. In stage III disease the choice in favour of radiotherapy is also guided by health economics considerations.

Larynx preservation trials have demonstrated that neo-adjuvant chemotherapy followed, in responders, by radiation therapy is as safe as strategies

based on upfront surgery. Functional larynx can be kept in 30–50% of the cases treated with organ preservation programmes and a significant reduction in distant metastases is usually reported for this type of sequential application of radio-chemotherapy.

Altered fractionation has been extensively investigated over the last two decades, using regimes ranging from strong acceleration to true hyperfractionation. Most of these altered dose schedules have yielded significant improvements in loco-regional control, generally of 10 to 15% compared to those observed after conventional fractionation, with interesting trends as regards survival rates. Severe late toxicity can be observed when strong acceleration regimes are used, especially when the inter-fraction time interval is <6 hours.

Concurrent radio-chemotherapy is now considered by many centers, and not by all, as the standard approach for locally advanced disease since it has been shown to affect significantly not only the loco-regional control but also the disease-free survival, as demonstrated by recent recta-analyses. Long-term toxicity still remains to document more extensively, especially as regards dose-schedules combining cytostatic drugs and altered fractionation.

Finally the increasing role of *re-treatments* with radiotherapy for both second primaries and recurrences is currently under investigation: encouraging results are now documented both as regards tumor long-term control and functional outcome.

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Intermittent CO2 or KTP laser surgery in combined treatment of head and neck cancer

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KTP (Potassium (K+)-Titanyl-Phosphate)-laser surgery in tumors of the oral cavity, the pharynx and hypopharynx allows an extended resection offering all the advantages of CO2 laser surgery with a more flexible handling during cutting with direct fiber contact to the tissue and coagulation without contact. A combined chemo-radiotherapy is started in our patients after panendoscopy with tattooing of the tumor margins and a complete staging. Mitomycin, 5-Fluorouracil and hyperfractionated radiation is performed up to 30 Gy in a first cycle. Then the CO2 or KTP-laser surgery is done in the old margins with preferation of the CO2 in the hypopharynx and the KTP laser in the oral cavity and oropharynx. Intermittent neck dissection follows this surgical procedure after a time interval of 10 to 14 days. Then the second cycle of chemoradiation completes the treatment. Bioptic controls follow these protocol after six and twelve weeks. In 20% of the patients treated no vital tumor cells could be found in the laser resected specimen any more. All the other resections were performed within healthy tissue borderlines. Tumor control in all cases including T3 stages could be performed by means of this technique with the advantage of no plastic reconstructive covering of the resection site and better functional outcome, especially for swallowing and no necessity for a tracheostomy.

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Helper-free generation of new oncotropic and oncotoxic vectors derived from MVM autonomous parvovirus

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Autonomous parvoviruses have several features that attracted attention to their potential use as vectors for cancer gene therapy. They have a strong oncotropism through targeting viral-gene and transgene expression to tumor cells, and their non-structural NS1 is responsible for their oncotoxicity. In addition, they are non pathogenic in adult animals, do not integrate into the host genome, are resistant to extreme pH and temperature conditions, are not inactivated by human complement, and, finally, seem to be associated with no or low immunogenicity. Their production was however difficult, their spontaneous titer after transfection was low ($10.E + 3 - 10.E + 4$ infectious units [iu]/ml) and stocks were contaminated by wild-type MVM that is generated through recombination between cotransfected vector and helper DNA sequences. We set up a method of concentration and purification, that allows to reach titers of $10.E + 9$ iu/ml. We also generated a packaging cell line by integrating helper sequences allowing to reach spontaneous recMVM titers of up to $10.E + 7$ iu per ml after three to four rounds of infection, with no concentration procedure. Although undetectable in the