and underestimate the effectiveness that may be afforded by the better regimens.

Even given these caveats, the Oxford meta-analysis is our best look into 2 decades of information from randomized trials of adjuvant therapy. The results presented at the September 2000 overview of the effectiveness of adjuvant therapy (tamoxifen and/or polychemotherapy) did not differ substantially from those presented in 1995 and published in 1998. They suggest that all major subsets of patients can expect a reduction in risk of recurrence and breast cancer related death from adjuvant therapy.

Approximate Proportional Risk Reductions For Mortality

Age		Tamoxifen	Chemo	Combined*
<50	ER+	25%	25%	45%
	ER−	0%	35%	−
>50	ER+	25%	10%	35%
	ER−	0%	20%	−

* Inferred given apparent independence of effects.

The Overview suggests that not all poly chemotherapy regimens are equivalent and in particular regimens that include an anthracycline seem better (with about a 16% additional proportional risk reduction) than regimens that do not. The reductions are modest, but important, particularly for women with moderate to high risk of recurrence. Of course for women with a low risk of recurrence and death the risks associated with adjuvant therapy may outweigh the benefit. More detailed information from the Oxford 2000 analyses will be presented, as well as a discussion of some probable important differences in different classes of adjuvant polychemotherapy regimens, and how this information might be used by the clinician.

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Colon cancer

Buyse Marc. *International Institute for Drug Development, Brussels, Belgium*

Background: Treatment of advanced colorectal cancer has made substantial progress recently. However, improvements in response rates have not always translated into significant survival benefits, which has raised doubts about the usefulness of tumour response as a clinical endpoint.

Methods: Meta-analyses were performed on individual data from 3,791 patients entered in 25 randomised trials comparing first line treatment with bolus intravenous 5-fluorouracil (5FU) ("bolus FU") with experimental treatments ("experimental FU") consisting of 5FU + leucovorin, 5FU + methotrexate, 5FU continuous infusion, or hepatic arterial infusion of 5-fluoro-2'deoxyuridine (FUDR). Two further meta-analyses comparing bolus FU +/− leucovorin to the same + a-interferon were used to validate the results on individual data from 3,254 patients.

Results: Compared with bolus FU, experimental FU led to significantly higher tumour response rates (odds ratio = 0.48, P < 0.001) and longer survival (hazard ratio = 0.90, P = 0.003). The survival benefits could be explained by the higher tumour response rates. However, a treatment that reduced the odds of failure to respond by 50% would be expected to reduce the odds of death by only 6%. In addition, less than half of the variability of the survival benefits in the 25 trials could be explained by the variability of the response benefits in these trials.

Conclusions: Increases in tumour response rate translate into small increases in survival for patients with advanced colorectal cancer. However, in the context of individual trials, knowledge of a treatment's benefit upon tumour response does not allow an accurate prediction of its ultimate benefit upon survival.

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Locally advanced head and neck cancer: meta-analysis of updated individual data

J.P. Pignon[1], B. Baujat[1], C. Hill[1], J. Bourhis[2]. *MACHNC Collaborative Group; [1] Institut Gustave Roussy, Dept of Biostatistics and Epidemiology, Villejuif, France; [2] Institut Gustave Roussy, Dpt of Radiation Oncology, Villejuif, France*

The MACH-NC study (Lancet 2000; 355:949) is based on the individual updated data collected on 10 741 patients in 63 randomized trials comparing loco-regional treatment to the same loco-regional treatment + chemotherapy (CT).

The relative risk of death (RR) with CT as compared to without was 0.90 (95% Confidence Interval (CI): 0.85-0.94). There was a significant heterogeneity between trials (p<0.0001). Using a graphical method, 5 trials (811 patients) were identified as major contributors to this heterogeneity. A sensitivity analysis showed that after exclusion of these 5 trials, the heterogeneity was no more significant (p=0.14) and the RR was practically unchanged (RR=0.91, 0.87-0.96).

The results of MACH-NC were statistically different according to the timing of CT (p=0.005). The five trials with outlying results included four trials with CT concomitant to radiotherapy and one trial with adjuvant CT. After exclusion of these 5 trials, the effect of CT timing was no longer significant (p=0.34), the RR for the adjuvant subgroup of trials decreased from 0.98 (CI=0.85-1.12) to 0.91 (0.78-1.06), the RR for the concomitant subgroup increased from 0.81 (CI=0.76-0.88) to 0.88 (CI=0.81-0.95) and the RR for neoadjuvant subgroup was unchanged (RR=0.95, CI=0.88-1.01).

Lastly, in the neoadjuvant group, there was a significant benefit of platin + 5-FU trials (HR=0.88, 0.79-0.97), significantly different (p=0.05) from the effect of other neoadjuvant CT (HR=1.01, 0.92-1.10).

In summary, the small benefit of chemotherapy observed in locally advanced head and neck cancer is robust to exclusion of outlying trial results. The results concerning the benefits of chemotherapy by timing are not. The planned update of MACH-NC which will add more than 25 trials and 8 000 patients will clarify this issue since most of these trials study chemotherapy given concomitantly with radiotherapy.

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Overview of rectal cancer trials

Richard Gray, Robert Hills, Joanna Marro, Rebecca Stowe. *University of Birmingham Clinical Trials Unit, Birmingham B15 2RR on behalf of the Colorectal Cancer Collaborative Group.*

Chemotherapy (CT) and radiotherapy (RT) have the potential to improve survival in rectal cancer. To help define the size of benefit achievable for different types of patient, and the optimal CT and RT regimens, a meta-analysis of all randomised trials of CT or RT, in colon and rectal cancer, was undertaken. Individual patient data were sought from all relevant studies starting before 1995. If individual patient data could not be obtained, information was abstracted from published data as far as possible. Individual patient data were available on 6633 patients in 14 trials of preoperative RT, and on 2157 patients in 8 trials of post-operative RT. Preoperative RT reduced the annual risk of local recurrence by 44% SD6 (p<0.00001) and postoperative RT reduced it by 33% SD11 (p=0.002). Overall survival was only marginally better among patients allocated RT but preoperative RT, at biological equivalent doses over 30Gy, reduced the risk of death from rectal cancer (22% SD5, p=0.00002) and, to a lesser extent, death from all causes (56.5% vs 58.9% dead; p=0.04). Data were available from 50 CT studies, involving 18,000 patients. Almost all CT regimens tested involved 5-fluorouracil (5-FU), with or without other drugs. Short bolus CT regimens appeared ineffective. Short portal vein infusional regimens may improve survival marginally. The largest benefits were seen in studies of prolonged 5-FU biomodulated by folinic acid (29%SD9;p=0.0007) or by levamisole (25%SD7;p=0.0003) but these studies included almost exclusively colon cancer patients. The mortality reductions in studies testing unmodulated 5-FU regimens were smaller (6%SD4;p=0.11) but appeared at least as large for rectal as colon cancer. There remain unanswered question, therefore, about CT for rectal cancer, in particular for node-negative patients.

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Radiation carcinogenesis

Elaine Ron. *National Cancer Institute, Bethesda, MD, USA*

Although cancer of the thyroid gland is relatively rare, it is by far, the most common malignancy of the endocrine system. External radiation is the only well established cause of thyroid cancer. Extensive information from studies of people exposed to medical irradiation, as well as the atomic bombings in Hiroshima and Nagasaki clearly demonstrates that the thyroid gland is highly sensitive to the carcinogenic effects of exposure to x- and γ radiation during childhood. Among people less than 20 years old at the time of exposure, the risk of developing thyroid cancer increases significantly with increasing radiation dose and decreasing age at exposure. The trend in risk with dose is consistent with linearity. Following radiation exposure, the elevated risk of thyroid cancer appears to continue throughout life, but there is some indication that the risk may be highest 15 to 19 years after exposure. Data regarding adult exposure are limited, but there is little evidence of an association between exposure after age 20 years and thyroid cancer risk. Investigations of patients examined or treated with radioactive iodine do not demonstrate a link between ^{131}I and the risk of thyroid cancer. However, the patients evaluated were almost all adults and, therefore, these

studies are not informative about risks from childhood exposure to ^{131}I. In contrast, very large increases in the incidence of childhood thyroid cancer have occurred following the Chernobyl accident. Data from the Ukraine, Belarus, and Russia suggest that the risks from childhood ^{131}I exposure are high and may not differ substantially from those associated with external radiation. To date, findings from studies of environmental radiation exposure are inconsistent. Additional data from studies of populations exposed to radiation from nuclear weapons testing and production in the former Soviet Union will become available in the near future. These data should help clarify the role of radionuclides in the etiology of thyroid cancer.

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Thyroid Carcinoma After Chernobyl

D. Williams. *University of Cambridge, Strangeways Research Laboratory, Cambridge, UK*

4 years after the world's worst nuclear accident at Chernobyl an excess of thyroid cancer cases was noted among children who had been exposed to fallout from the disaster. That increase has continued and new cases are still being seen in those who were children at the time of the accident. It is now 15 years since the accident, and so far approaching 2000 cases of thyroid cancer have occurred in the affected area, which involves most of Belarus, the northern part of Ukraine and a small part of the Russian Federation. Collaborative research to study these cases is ongoing, the results so far show that the diagnoses of thyroid cancer are substantiated, with many of the early cases showing marked local invasion. The increase is almost exclusively in papillary carcinoma, so far very few follicular or medullary carcinomas have occurred, there are no reliable reports of increases in non thyroid malignancies, although these cannot yet be entirely excluded. The increase is very largely in those who were children at the time of the accident, with a very marked association of age with sensitivity. The findings after Chernobyl differ greatly from those after the atomic bomb explosion. In Japan the exposure was very largely to whole body radiation from gamma rays and neutrons. After Chernobyl the exposure was to isotopes in fallout, and apart from the inert gas xenon, the largest components were radioactive isotopes of iodine (including Tellurium 132 which decays to Iodine 132).

Exposure to isotopes of iodine gives the thyroid over a 1000 times the average dose to the rest of the body, explaining the specificity for thyroid cancer. Radiation is particularly effective in inducing double strand breaks in DNA, and papillary carcinoma is linked to rearrangement in the ret oncogene, providing an explanation for the specificity for papillary carcinoma, although follicular carcinoma may still show a rise in incidence with a longer latent period than papillary carcinoma. The particular sensitivity of children can be linked to a combination of a higher thyroid dose and the biology of thyroid growth, which falls to a very low level in adult life. The post Chernobyl thyroid carcinomas form the largest group of human tumours of one type, due to a known cause on a known date; to facilitate study of the changes that lead to radiation induced carcinogenesis an international tumour bank has been created. Currently this holds extracted nucleic acids from several hundred tumours and these are now available for study by approved projects. Chernobyl was a major disaster for the population exposed, and for the economies of the countries involved, particularly Belarus. Few of the patients with thyroid cancer have died from the disease, but help is still needed in the affected areas, and continuing study of the occurrence of thyroid cancer and surveillance for other possible effects remains essential.

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Prognostic factors, treatment and follow-up of patients with papillary (PTC) and follicular (FTC) thyroid carcinoma

Martin Schlumberger. *Institut Gustave Roussy, Villejuif, France*

Prognostic factors for PTC and FTC include age at initial treatment, tumor burden (tumor size, extrathyoid extension, lymph node metastases, distant metastases) and tumor histotype.

More than 85% of PTC and FTC patients belong to a low risk group, with specific mortality rates below 2% at 25 y and can be individualized at the time of initial treatment by using the TNM or MACIS scoring systems.

Initial treatment includes surgery (near-total thyroidectomy and in case of PTC central neck dissection). A lobectomy may be sufficient for unifocal micro-PTC and for small minimally invasive FTC. Post-operative radioiodine ablation is performed selectively, i.e. only in high risk patients. Then, levothyroxine treatment is given to all patients with PTC and FTC with the aim to decrease serum TSH to low level.

The search for persistent or recurrent disease is based on neck ultrasonography, serum thyroglobulin (Tg) determination and total body scanning with radioiodine (131I). TSH stimulation can be obtained either by withdrawing levothyroxine therapy for 4 weeks or by intra-muscular injections of recombinant human TSH.

Neck recurrences are treated with 131I and surgery, typically using an intra-operative probe. Lung metastases are treated with 131I in case of uptake; and bone metastases are treated by surgery when feasible, followed by radioiodine and external radiotherapy; embolisation and cement injections may also be useful. Bio- and chemotherapy are not effective and should be given only to patients with progressive disease in the frame of controlled trials.

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Prophylactic surgery in patients with multiple endocrine neoplasia type 2a

S. Wells[1], J. Moley[2], M. Skinner[1], M. DeBenedetti[2]. [1] *Duke University, Surgery, Durham, USA;* [2] *Washington University, Surgery, St. Louis, USA*

Patients with the type 2 Multiple Endocrine Neoplasia(MEN)syndromes, MEN 2a, MEN 2b and Familial Medullary Thyroid Carcinoma(FMTC)inherit dominant/negative mutations in the RET protooncogene. The diseases have distinguishing phenotypes,which are characterized by medullary thyroid carcinoma,(MEN 2a, MEN 2b and FMTC)pheochromocytomas(MEN 2a and MEN 2b), hyperparathyroidism (MEN2a) and a generalized neural hypertrophy (MEN 2b). Virtually all patients with these syndromes express medullary thyroid carcinoma (MTC), which is the most common cause of death.

However, the time of onset and the biological agressiveness of the MTC vary, being earlier and more rapid in patients with MEN 2b but later and more indolent in patients with FMTC. The MTC cells secret calcitonin (CT), which is an excellent tumor marker. With direct DNA analysis for mutations in the RET protooncogene it became possible to detect members of MEN 2a, MEN 2b or FMTC kindreds who had inherited a mutated alleal. We advised total thyroidectomy in family members who had distinctive RET mutations. The operation was a total thryoidectomy with removal of lymph nodes in the central zone of the neck. Stimulated plasma CT levels were determined before and immediately after surgery, and at yearly intervals thereafter. Since 1970 we have accrued 83 families (1186 patients) with MEN 2a,38 families (57 patients) with MEN 2b and 9 families (147 patients) with FMTC. We have performed thyroidectomies on 83 patients based on genetic testing. Postoperative evaluation ranges from one month to eight years (mean 4.6 years). Preoperative stimulated plasma CT levels were in the normal range in 30 (36%) patients and in 75 (90%) patients stimulated plasma CT levels were in the normal range, postoperatively. On histologic evaluation of thyroidectomy specimens in 5(6%) patients had no evidence of a C-Cell disorder and in 16 (19%) patients only C-Cell hyperplasia was present. In MEN 2a, MEN 2b or FMTC direct DNA analysis for mutations in the RET protooncogene is the method of choice for identifying kindred members who have inherited a mutated alleal. Measurement of stimulated plasma CT levels in the postoperative period is an excellent method of determining the success of the surgery and for evaluating recurrent and persistent disease. In this setting total thyroidectomy appears to be curative in patients with early disease and represents a model of preventative oncology.

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Low dose hyper-radiosensitivity

M.C. Joiner[1], S.C. Short[2], B. Marples[1], M.I. Saunders[2]. [1] *Gray Cancer Institute, Northwood, United Kingdom;* [2] *Mount Vernon Hospital, Northwood, United Kingdom*

Purpose: To review the phenomena of low-dose hyper-radiosensitivity (HRS) and increased radioresistance (IRR) and explore the possible impact of HRS on clinical radiotherapy. Materials and Methods: Clonogenic survival of cell populations has been determined accurately by automated microscopy or FACS. Experiments have been carried out on more than 45 cell lines, altering the size, timing and dose rate of one or more radiation exposures. The effect of HRS has also been determined in mouse normal-tissue models and in human tumour xenografts. Measurements of basal-cell density have been made in skin biopsies exposed to successive small radiation doses from patients undergoing radiotherapy. Results: HRS has been demonstrated in more than 78% of the cell lines tested. It also occurs in some tumours and normal tissues in vivo. It produces increased cell kill per unit dose at doses below one gray which is more apparent in more radioresistant cell lines compared with both sensitive cell lines and