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

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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

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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

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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

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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