An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer

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Summary Meta-analysis of the published results from 54 randomised controlled trials of adjuvant chemotherapy in head and neck cancer suggests that chemotherapy might increase absolute survival by 6.5% (95% confidence interval 3.1-9.9%). The odds ratio in favour of chemotherapy is 1.37 (95% confidence interval 1.24-1.5). Single-agent chemotherapy given synchronously with radiotherapy increased survival by 12.1% (95% confidence interval 5-19%). The benefit from neoadjuvant chemotherapy was less: a rate difference of 3.7% (95% confidence interval 0.9-6.5%). The results suggest that the investigation of optimal agents and scheduling for synchronous radiotherapy and chemotherapy might still be important in clinical trials in head and neck cancer.

Keywords: overview; randomised trials; head and neck cancer

Attitudes towards cytotoxic chemotherapy for squamous carcinomas of the head and neck range from enthusiasm (Dimery and Hong, 1993) to disdain (Tannock and Brownman, 1986; Taylor, 1987). Response rates to chemotherapy are high, but this responsiveness does not appear to translate into durable benefit in terms of survival. Recent meta-analyses of adjuvant chemotherapy for squamous cell carcinoma of the head and neck failed to show any benefit from such treatment (Stell and Rawson, 1990; Stell, 1992). However, several randomised trials published subsequently have been reported as showing benefit from adding chemotherapy to standard therapy. In order better to define the possible role for chemotherapy and to suggest possibly fruitful avenues for exploration, a further meta-analysis of published randomised clinical studies of adjuvant chemotherapy in head and neck cancer has been performed.

The primary purpose of this overview was to discover whether the addition of chemotherapy to definitive standard therapy improved survival in patients with cancer of the head and neck. Secondary objectives included an assessment of whether the timing of chemotherapy, before, during or after standard therapy, was important; a specific assessment of the effectiveness of platinum/5-fluorouracil (5-FU) regimens; an evaluation of single-agent chemotherapy given synchronously with radiotherapy; an assessment of the effect of chemotherapy upon locoregional control rates; an assessment of the effect of chemotherapy upon the occurrence of distant metastases.

Materials and methods

A structured search was conducted to identify randomised clinical trials of chemotherapy in head and neck cancer. A trial was suitable for inclusion if it fulfilled the following criteria:

- published between January 1963 and August 1993;
- allocation of treatment was said to be randomised;
- there was a control arm in which patients did not receive chemotherapy;
- Results were available for survival, disease-free survival or local control.

Abstracts as well as published papers were acceptable. If the same data had been published more than once, the most recent data were used. Several complementary search procedures were used: MEDLINE search; a review of the Physicians' Data Query (Silver Platter) clinical trials data base; review of the relevant sections in the two available volumes of Randomized Trials in Cancer: A Critical Review by Sites (Cachin, 1978; Dodion et al., 1986); a systematic review of every volume of the published proceedings of the American Society of Clinical Oncologists from 1979 to 1993.

The data were abstracted from photocopies of the original publications and entered onto a spreadsheet (Excel 4.0). Trials were classified as follows:

- neoadjuvant, chemotherapy given before definitive therapy;
- synchronous, chemotherapy given synchronously with radiotherapy;
- post-definitive, chemotherapy given after definitive therapy.

Some trials combined more than one of the above components; such trials were classified according to the earliest appearance of chemotherapy in the protocol. For example, a trial involving two courses of chemotherapy then surgery, then maintenance chemotherapy would simply be classified as neoadjuvant.

The analysis was performed on published data: no attempt was made to obtain data on individual patients. The times at which survival was reported varied between studies. The maximum survival interval available was used with an upper limit of 5 years. Survival data, therefore, apply only to the particular time point available for each trial. No allowance has been made for the inevitable censoring within trials or for differential censoring between trials. Wherever possible, the raw numbers were used; in the absence of such data the numbers were estimated from the published survival curves. The values were obtained by applying a set square to the survival curve at the specified time point, reading off the percentage surviving, and thereby calculating, from the total number randomised to that group, the absolute number of survivors. The validity of the abstracted data was assessed by repeated cross-checking and also, where possible, by comparison with the data presented in previous overviews (Stell and Rawson, 1990; Stell, 1992). Of necessity, however, the data used are crude and, at best, approximate.

The estimation of the number of events in the control and experimental arms is, when there is no access to data on individual patients, subject to a number of possible biases. Two possible sources of bias are: differential censoring between the two arms of the trial so that the denominator in the experimental arm is proportionally lower than that in the control arm, thereby exaggerating the benefit of the experimental therapy; and systematic errors in the data from published reports so that the survival rate is consistently overestimated in the experimental arm and consistently underestimated in the control arm. Sensitivity
analyses have been used to investigate the possible effects of this type of bias upon the conclusions. Two approaches were used. In the first approach the number of survivors in the experimental group was decreased, and the number of survivors in the control group increased by a constant percentage for all trials. The second approach was similar except that, instead of a fixed percentage correction being applied to all trials, a different percentage correction was applied to each trial. This correction varied randomly within specified limits. The first approach gives an indication of the robustness of any conclusions, while the second method perhaps reflects more accurately the true distribution of any bias that may arise. The calculations were as follows. If there were 60 estimated survivors in the group treated with chemotherapy and 40 estimated survivors in the control group, and the bias was 5%, the adjusted survival estimates were:

- chemotherapy group: 60 - (0.05 × 60) = 60 - 3 = 57
- control group: 40 + (0.05 × 40) = 40 + 2 = 42

A further bias arises from the assumption, necessary for the approach adopted in this paper, that the extracted data are binomially distributed. The consequence is that the estimated variances will be less than the true variances.

Statistical methods

This meta-analysis has used two different statistical methods for pooling data: the odds ratio method of Mantel–Haenszel (Early Breast Cancer Trialists’ Collaborative Group, 1990) and the rate difference method described by DerSimonian and Laird (1986). The homogeneity and heterogeneity of the pooled studies have been assessed both graphically and by the Q-statistic (DerSimonian and Laird, 1986). Multiple comparisons have been made, in the subgroup analyses, and therefore conservative P-values should be used for assessing significance.

The problem of publication bias has been addressed using sensitivity analysis. The single large trial method ascertains the number of patients that would be required to overturn the positive conclusion from a meta-analysis were there to be a negative trial that had not been identified for inclusion in the analysis. A similar approach is to estimate the number of clinical trials of achievable size that would be required to negate a positive conclusion. A further technique assesses the possibility that a single positive trial might dominate the analysis: positive trials are excluded sequentially, and in combination, from the analysis and the effects upon the overall conclusion are assessed.

The probability that a negative study is falsely negative has been assessed using the method published by Detsky and Sackett (1985). This method incorporates the advantage of retrospective review: since the event rate in the control arm is known, fewer assumptions are required than in methods designed to assess power and sample size prospectively.

Results

Over 150 randomised trials in head and neck cancer were identified. Of these, 54 fulfilled the criteria for inclusion in this meta-analysis. These are summarised in Table I. The time at which the end point was assessed was unspecified in 9/54 studies and was less than 24 months in a further nine studies. The graphical assessment of homogeneity for the 51 comparisons of survival data is shown in Figure 1. The trials appear to be heterogeneous, and this is confirmed by the Q-statistic of 111.1 which, on 50 degrees of freedom, corresponds to a P-value of <10^{-6}: we can reject the null hypothesis of homogeneity among trials. This degree of inhomogeneity is unsurprising given the wide variations in eligibility criteria and times chosen for the estimation of survival.

The data for all 51 comparisons are presented in Table II. The odds ratio, rate difference, χ^2 for difference in survival between treatment and control arms and P-value calculated from χ^2 are shown for each trial. Using P<0.05 as the criterion for a positive result, only nine studies were positive by both the rate difference and odds ratio methods; 39 were negative by both methods and three were positive by the odds ratio method but negative by the rate difference method. For trials defined as non-significant (P>0.05), the probability that the result is a false negative has been shown for a 25% relative increase in survival in the chemotherapy arm. A relative increase in survival of 25% corresponds to an increase, in absolute terms, from 40% to 50% or from 16% to 20%. Of the 42 negative comparisons, 14 had a >25% probability of being false negative and five had a probability of being false negative of >50%.

The 95% confidence limits of the rate differences are shown in Figure 2. Trials lying above the zero axis indicate possible benefit from chemotherapy; trials lying below it indicate a disadvantage from chemotherapy. Trials whose confidence limits straddle the zero axis are, by this method, non-significant at the 0.05 level of significance. Figure 3 uses a similar convention, but this time trials analysed by separate categories: neoadjuvant studies; synchronous studies using single agents; and studies using platinum-5-FU combination chemotherapy.

Table III shows the pooled estimates for odds ratio and rate difference and their confidence limits. The table also includes χ^2 for difference between the control and treatment groups in terms of the end point specified, and Q-statistics (for homogeneity). Data are shown for survival for the whole group, and for the subgroups. Data on local control were useful in the analysis, and the data on distant metastases were available for 29 studies. These data are also shown in Table III.

The meta-analysis shows that chemotherapy produces a small, but clinically significant, improvement in survival: 6.9% with 95% confidence limits of 3.4% and 10.3%. The difference is statistically highly significant, P<10^{-10}. This conclusion is relatively insensitive to publication bias. Sensi-
| Ref | Eligibility | Treatment in experimental group | Treatment in control group | nc | ne | surv | es | ox |
|-----|-------------|---------------------------------|----------------------------|----|----|------|----|----|
| 1   | Non-metastatic carcinoma of the head and neck | ia mtx for 25 - 40 days then xrt | xrt 70 - 75 Gy | 72 | 70 | 60 months | 31 | 18 |
| 2   | III IV SCC head and neck | plat day 1 of each xrt week (7 to 9 doses) | 54 Gy or 1.7 Gy pf 5F pm max 65 74 | 39 | 45 | 24 months | 30 | 20 |
| 3   | O Op N H L SCC 12 n2 3 13 n1 3 14 n0 3 m0 | vcr/adr/belo/mtx/5fu/ohure 6mp then xrt(7) then chemo during split then che mo x1 after xrt | 32.5 Gy/13F rest 3w 32.5 Gy 13F | 30 | 28 | 12 months | 6 | 2 |
| 4   | t3mx mo oral cavity | mtx belo vcr post surgery | xrt post surgery | 16 | 16 | 36 months | 5 | 10 |
| 5   | adv III & IV hn sec fit for cur xrt O Op L H | 5fu(1 - 3) first and 3rd week of xrt | xrt 66 Gy/37.5 Gy & saline placebo as for 5fu schedule | 88 | 87 | 36 months | 49/60 | 37/49 |
| 6   | III IV O Op L H | plat (1 - 4) belo (1 - 4) vinde 31 (1 - 4) q21 then 2/52 then xrt | 50 - 55 Gy at 1.8 Gy pf to 2 then as xrt 65 - 75 Gy | 48 | 52 | 42 months | 10 | 12 |
| 7a  | adv soc hn | 6mp + xrt | otherwise soc | 11 | 9 | 12 months | 3 | 4 |
| 7b  | adv soc hn | ia mtx + FA | xrt alone | 9 | 4 | 12 months | 9 | 4 |
| 8   | SCC Op 7 = 72 or any infiltrative M0 | mtx + belo iv or im x2 pw for 5w | xrt 70 Gy in 7 - 8.5w | 9 | 25 | 60 months | 24 | 21 |
| 9   | SCC local 11 4n0 3 n O OP H L | mtx for 15d then xrt | xrt 55 80 Gy in 5 10w | 312 | 326 | 60 months | 79 | 75 |
| 10  | t3 t4 soc pharynx | 5fu (1 - 5) xrt 2 Gy pf (5 - 8) 5fu x2 pw during xrt to toxicity xrt total 30/6 | 60 - 75 Gy 30 - 37f 6 7w | 17 | 15 | 12 months | 14 | 7 |
| 11  | inop III IV | belo x2 pw during xrt then maintain belo + mtx q/10 x16w | xrt 70 Gy at 1.8 Gy pf 5f pw | 52 | 52 | 36 months | 22 | 12 |
| 25  | subset of OOp from above updated | xrt + 5fu (1 - 4) then x3 pw during xrt (6 - 7w) 5fu stopped if toxicity | xrt 60 - 70 Gy in 6 - 7w | 86 | 68 | 60 months | 9 | 6 |
| 12  | SCC adv pot curable by xrt < 80 O Op N S L | xrt + 5fu (1 - 4) then x3 pw during xrt (6 - 7w) 5fu stopped if toxicity | xrt 60 - 70 Gy in 6 - 7w | 68 | 68 | 42 months | 24 | 15 |
| 13  | SCC mO < 75 T2 3T0 2 4OP T3 4L ALL | mtx (6 0 14) + xrt 40 - 55 Gy in 15 - 16f in 3w | xrt alone | 156 | 157 | 8 - 79 months | 68 | 81 |
| 14a | untreated resectable II H III IV OOpH L | induction plat (1) belo (7 - 3) | surgery & post op xrt 50 Gy 5w or 60 Gy 6w (residual disease) | 140 | 152 | 60 months | 52 | 53 |
| 14b | untreated resectable II H III IV OOpH L | as above induction then + xrt then maintenance plat 80(1) q28 x6 | surgery & post op xrt 50 Gy 5w or 60 Gy 6w (residual disease) | 151 | 152 | 60 months | 68 | 53 |
| 15  | St II IV OOp N nose H (not St III tonsil or t3 L m0) | belo (1 - 4) cyclo (1 - 5) mtx (1) + (5) 5fu (1 - 5) x2 q21 then standard Rx | preop xrt + xrt or xrt ± node dissection | 30 | 39 | 24 months | 14 | 16 |
| 16  | adv soc hn | xrt 45 Gy in 4.5 w to 75 Gy in 9.5 w + oral urea mon wed fri during xrt | xrt alone | 24 | 16 | 24 months | 7 | 4 |
| 17  | Op H L O (3 4 2 1 2 12 H) | plat (1 - 3) 5fu (1 - 5) vinde 11 (1 5) then 3w then xrt | xrt 55 Gy then assess if > 50% reg then to 70 Gy | 55 | 53 | 36 months | 31 | 29 |
| 18  | pyriform fossa t2 t3 n0 n1 n3 resectable | vcr (1) belo (4) mtx (1 2 2) then surgery then xrt 65 Gy | otherwise soc | 39 | 39 | 24 months | 14 | 16 |
| 19  | operable soc preop EOL | belo x3 pw 1hr before xrt | soc xrt + xrt only | 15 | 18 | 24 months | 14 | 17 |
| 20  | L (4 4 1 11 4n0 3 n0 3) | MMC (1 8 3) 5fu (1 - 4) (43 46) xrt 25 Gy 12F 2w (1 1 4) 25 Gy 10F 2w (3 5) | xrt 25 Gy/10F2w 4w gap 25 Gy/10F2w | 104 | 105 | 60 months | 42 | 42 |
| 21  | adv soc | plat (1) 5fu (1 - 4) q 28 during xrt | xrt 20 Gy 1.5 Gy pf (bd) 2w gap then 20 Gy 1.5 Gy pf (bd) | 11 | 18 | 12 months | n/s | n/s |
| 22  | st III IV | mtx (1 - 5) then day 15 start xrt at 2 Gy of x5 pw to mucosal tolerance (ave 63 Gy in 4.5d) | xrt alone at 2 Gy pf daily to 60 Gy total | 11 | 11 | n/s | n/s | n/s |
| 23a | adv unresectable II IV S O Op H L | mtx (1) (5) (9) then xrt | xrt 60 - 66 Gy in 6 - 6.5w at 10 Gy pw | 20 | 20 | 36 months | 4 | 5 |
| 23b | adv unresectable II IV S O Op H L | mtx (1) then xrt | xrt 60 - 66 Gy in 6 - 6.5w at 10 Gy pw | 28 | 28 | 36 months | 5 | 5 |
| 24a | resectable SCC III IV L O Op H II IV H III IV L | plat (1) 5fu (1 - 5) q21 (3) then xrt | xrt (low risk) 50 - 54 Gy pf (high risk) 60 Gy 1.8 Gy pf | 222 | 224 | 48 months | 102 | 85 |
| 25a | sec any t n3 t3 1 n4 any n | mtx (1) (4) (9) (12) (15) then xrt (ave 63.6 Gy) | xrt ± xrt dose ave 64.2 Gy | 36 | 39 | 36 months | 7 | 4 |
| 25b | sec O Op H L | carbop (1) 5fu (1 - 5) q21 then xrt + /- xrt | xrt + xrt xrt alone if cr to chemo | 108 | 110 | 24 months | 70 | 66 |
| 29a | sec O Op | belo (3) mtx (2) 5fu (2) plat (4) then | xrt + xrt xrt alone | 54 | 53 | 24 months | 21 | 22 |
| 27  | III III IV O Op H II IV III L | plat (1) 5fu (1 - 5) q21 x3 (or switch after 2) then local rx | xrt 70 Gy 1.8 Gy pf 8W or xrt + post xrt | 37 | 38 | 24 months | 23 | 18 |
| Ref | Eligibility | Treatment in experimental group | Treatment in control group | ne | nC | surv | ex | cs |
|-----|-------------|---------------------------------|-----------------------------|----|----|------|----|----|
| 30  | unrespectable III 1V scc < 76 Op H O L | (1-5) F5a (1-5) Q21 20 Gy xrt x3 in c-rx|x-3-c-rx-c-xrt-c | 70 Gy x1.8 Gy to 2 Gy pf | 80 | 77 | 36 months | 32 | 23 |
| 31  | O Op N H L 121314 | Chemo then xrt 15 19 24/10/100 then chemo 29 then xrt 43 47/20/40 then chemo 57 onwards | 2/day 24 Gy/100/100 then 2/4 then 24 Gy/100/100 | 23 | 13 | 12 months | 8 | 2 |
| 32  | St III and IV | (1-5) F5a (1-5) Q21 x4 xrt | xrt: srg + 60 Gy (op) xrt 65 Gy (inop) | 118 | 119 | 36 months | 34 | 24 |
| 33  | t3 4-mtx to tx n2 -3 primary or recurrent scc O Op | (1-2)(5-6) B5o (2-5) Q20 x3 (10-4) xrt 28 or 35 then srg if poss then 40 - 50 Gy | srg if poss then 50 - 60 Gy; if inop then up to 70 Gy | 31 | 28 | 40 months | 14 | 6 |
| 34  | scc IV unrespectable male ml0 | vcr + mtx + F A q 21d s xrt | xrt 70 Gy/7w | 12 | 11 | 24 months | 1 | 1 |
| 35  | resectable curable scc h n excl sal | mtx escalating wkl y x4 then (not N) then mtx q7d x4 then mtx x7 x8 (op xrt mtx x12) | srg (not N) + xrt 60 - 65 Gy at 1.8 to 2 Gy pf | 32 | 28 | 40 months | 16 | 14 |
| 36  | O (tongue, floor of mouth, soft pal, rmt, buccal mucosa) | mtx in stop at tow 2 w gap then 30 Gy in 2w ass' s or on to 60 Gy | xrt alone 30 Gy ass then s or on to 60 Gy | 21 | 18 | 18 months | 4 | 3 |
| 37  | ca h n Op N L H Sal S | ohurea po every 3d during xrt | xrt only wide dose range 40 - 90 Gy | 9 | 7 | n/s | n/s | n/s |
| 38  | N SCC ml0 | if or good pr to xrt ass at 65d vcr (1) cyclo 1-4) adr 1-28 x12 (planned but revisted to 6) | xrt 60 Gy/2 Gy pf/6w | 113 | 116 | 48 months | 66 | 76 |
| 39  | t3 14-50 - n3 mo scc | xrt 60/2/6 synchron 5 fu every 2 iv x2 | xrt 60 Gy/2 Gy pf/6w | 300 | 277 | 60 months | 180 | 9 |
| 40  | st III IV Op L H | (1)(1) mtx (1-8) vcr (1) Q21 x3 then srg day 84 (s + post op xrt) | surgery then xrt | 82 | 76 | 60 months | 23 | 24 |
| 41  | a2a (t3 4-56 - 2 scc buccal mo | b5o x3 x view during xrt 55 60 in 7w 3f pw (b5o given on non xrt days) | xrt 55 - 60 Gy 3f pw (2.85 to 3.05 Gy pf) 7w | 64 | 52 | 60 months | 38 | 12 |
| 42  | b2b (t3 4-56 - 2 scc buccal mo | b5o q 4d x4 then xrt + b5o x1 | xrt 55 - 60 Gy 3f pw (2.85 to 3.05 Gy pf) 7w | 20 | 20 | n/s | n/s | n/s |
| 43a | Opt (tongue base) | vcr b5o mtx mm 5fu x2 then xrt | xrt | 23 | 19 | n/s | n/s | n/s |
| 43b | Opt (tongue base) | xrt + syn b5o | vcr xrt + im 5fu | 19 | 19 | n/s | n/s | n/s |
| 44  | max sinus | convex xrt + im 5fu | convex xrt | 25 | 38 | 12 months | 21 | 23 |
| 45  | st III IV scc (1) or 14 Op H L n x n | vcr ohobert + mtx 5fu + ohb ohurea tmp cyclo iv xrt (28) Q21 x1 | xrt only 40 - 60 Gy in 3 6w | 46 | 39 | 60 months | 11 | 10 |
| 46  | st III IV scc (1) or 14 Op H L n x n | xrt + Ohurea x2 pw | xrt only 40 - 60 Gy in 3 6w | 75 | 75 | 60 months | 5 | 13 |
| 47  | L 14 or n3 H all t3 14 or n3 adv O Op N E | vbl/b5o/mtx/cyclo 5fu then xrt/srg then chemo x6 | xrt w/ or srg alone | 33 | 35 | 24 months | 13 | 18 |
| 48  | scc ant tongue floor of mouth | mtx Q28 x4 inf with FA + b5o pm in 2x mtx b5o given after defin rx | defin rx only | 32 | 33 | 48 months | 19 | 19 |
| 49  | st II III poor prog sec h n | mtx imt (1) (5) then 252 then 1r then 6w then adj mtx or pla/adr | xrt (> 65 Gy in 2 Gy pf in 6.5w) or xrt choice made before rand | 41 | 41 | 60 months | 15 | 16 |
| 50  | st III & IV | mtx px a72 (2) Q7 d x7 d + post srg px | xrt alone 70 Gy 2 Gy pf 7w or preop xrt 50 Gy x2 Gy pf in 5w | 30 | 33 | 24 months | 19 | 18 |
| 51  | st III IV scc (1) or 14 Op N H L | (1) F5a (1-5) Q21 x2 x3 then conv rx | in 5w | 166 | 166 | 48 months | 101 | 108 |
| 52  | st III IV scc (1) or 14 Op N H L | (1) F5a (1-5) Q21 x2 x3 depending on resp > - PR to xrt 66 76 Gy | surg + 50 - 60 Gy depending upon margins | 111 | 111 | 60 months | 42 | 47 |
| 53  | scx h nl | b5o x1 before each frac xrt until toxicity | xrt alone 65 Gy in 6 - 7w | 24 | 22 | n/s | n/s | n/s |
| 54a | buccal mucosa t3 14 m0 | 5fu iv 1-1 xrt starts day 10 | xrt only 65 Gy in 6w | 21 | 22 | n/s | n/s | n/s |
| 54b | buccal mucosa t3 14 m0 | iudr iv 1-1 xrt starts day 10 | xrt only 65 Gy in 6w | 20 | 22 | n/s | n/s | n/s |
| 55  | buccal mucosa t3 14 m0 | mtx x1 1-1 xrt starts day 10 | xrt only 65 Gy in 6w | 59 | 61 | 60 months | 27 | 24 |
| 56  | scx Op L H L 111 n2 31 n2 1314 | mitomycin c on day 5 of xrt (adv pts further post xrt at 6w) xrt 66 67.7 at 2pf | xrt alone 59 - 67.65 Gy | 56 | 57 | 60 months | 27 | 24 |

Abbreviations: ne, number of patients in experimental group; nC, number of patients in control group; srg, t, time at which survival assessment was made; ex, number of survivors in experimental group; cs, number of survivors in control group; ca, carcinoma; scc, squamous cell carcinoma; h, head and neck; inop, inoperable; adv, advanced; n/s, not specified; tox, toxicity; O, oral cavity; Op, oropharynx; N, nasopharynx; H, hypopharynx; L, larynx; Sal, salivary gland; E, ear; rmt, retromolar trigone; ass, assessment; inop, inoperable, rand, randomisation; adj, adjuvant; conv, conventional; resp, response, regre, regression; nr, no response; cr, complete response; pr, partial response; def, definitive; Lrt, Locoregional treatment; pf, per fraction; pw, per week; frac, fraction; xrt, radiotherapy; po, orally; iv, intravenously; ia, intra-arterially; im, intramuscularly; syn, synchronously; maint, maintenance; pot, potentially; cur, curative; srg, surgery; mtx, methotrexa; carbo, carboplatin, plat, cisplatinum, 5fu, 5 fluorouracil; OHcort, hydrocortisone; adr, doxorubicin; OHurea, hydroxurea; bleo, bleomycin; cyclo, cyclophosphamide; bmp, 6 mercaptopurine; methpred, methylprednisolone; FA, folic acid; vcr, vincristine.
Table II Summary of survival data for the 51 comparisons

| Trial | Type | No. of pts | Rate diff | RD | OR ratio | OR ratio | Chi sq | P for sig. | PFN |
|-------|------|------------|-----------|----|----------|----------|--------|------------|-----|
| 1     | p    | 45         | -0.02     | 0.65 | 1.03     | 0.40     | 0.12   | 0.68       | 0.14|
| 2     | s    | 50         | -0.01     | 0.08 | 1.12     | 0.44     | 0.12   | 0.68       | 0.14|

RD, rate difference; OR, Odds ratio; low, high, 95% confidence limits; Chi sq, $\chi^2$ for significance; PFN, Probability that a trial is false negative, given a 25% relative survival benefit for chemotherapy.

Table III Summary of pooled data

| Group | No. of studies | No. of patients | Pooled RD (%) | Low (%) | High (%) | Pooled OR | Low high | Chi squared | P | Q |
|-------|----------------|-----------------|---------------|---------|----------|-----------|----------|-------------|---|---|
| All survival | 52 | 7443 | 6.5 | 3.1 | 9.9 | 1.37 | 1.24 | 1.5 | 39.6 | 1E-09 | 117 |
| All (larcophageal control) | 43 | 5389 | 7.9 | 1.9 | 13.9 | 1.44 | 1.28 | 1.63 | 37.2 | 1E-08 | 256 |
| All (distant metastases) | 29 | 4883 | -1.9 | -4.8 | 1.1 | 0.79 | 0.67 | 1.39 | 8.02 | 0.02 | 64 |
| Platinum/5FU (survival) | 8 | 1636 | 10.1 | -4.7 | 25.0 | 1.56 | 0.81 | 2.99 | 4.91 | 0.025 | 11 |
| Neoadjuvant (survival) | 28 | 4147 | 3.75 | 0.9 | 6.5 | 1.21 | 1.04 | 3.75 | 61.0 | 1E-11 | 20 |
| Synchronous single agent | 16 | 2506 | 12.1 | 5.0 | 19.0 | 1.77 | 1.51 | 2.1 | 54.7 | 1E-12 | 66 |

Chi squared is for significance. Q is for homogeneity and is analogous to a $\chi^2$ on (n-1) degrees of freedom, where n is the number of studies. The null hypothesis is that the trials are homogeneous. Low and high refer to the lower and upper bounds of the 95% confidence interval.
tivity analyses show that to overturn this positive conclusion would require:

- an unreported trial containing 800 patients with 25% survival in the chemotherapy group and 75% survival in the control group.

or

- an unreported trial with 50% survival rate in each arm and more than 20,000 patients randomised.

Even adding 20 negative studies with survival rates of 33% in each arm and 1200 patients randomised in each trial, the overall $\chi^2$ would still be 9.71 ($P < 0.005$). No single study was unduly influential. Eliminating significant studies in sequence did not affect the conclusions. For example, even if the 11 most significant studies were eliminated completely, the overall $\chi^2$ was still 5.29 ($P = 0.021$).

The results from the sensitivity analyses dealing with possible bias in data publication and extraction are shown in Figure 4. The robustness of the conclusion is sensitive to this type of bias. A constant bias of 5% produces results similar to a bias varying randomly for each trial between 0 and 10%; this again suggests that no one trial is unduly influential.

The subgroup analyses suggest that single-agent chemotherapy given with radiotherapy is particularly effective – rate difference 13.7% (95% CI 6.1–21.3%) – but neoadjuvant chemotherapy is somewhat less effective – rate difference 3.9% (95% CI 1.1–6.7%). Platinum/5-FU regimens do not appear to be outstandingly effective – rate difference 5.4% (95% CI 0.1–10%). The data on local control are consistent with the data on survival. The data on distant metastases are, in this respect, less consistent.

Discussion

This overview of trials of adjuvant chemotherapy in head and neck cancer suggests that chemotherapy might improve survival and that this improvement is more apparent for single-agent chemotherapy given synchronously with radiotherapy. Since two previous meta-analyses (Stell and Rawson, 1990; Stell, 1992) failed to show benefit from chemotherapy, the discrepancies between these previous analyses and the current results must be explained. Stell and Rawson’s first analysis (1990) included 23 trials, and the updated analysis added five newer trials to give a total of 28 trials (Stell, 1992). The recent flurry of trial publication means that there are now many more trials for analysis: 31 comparisons for survival effect. The second overview was not particularly robust: the $z$-value for overall survival was 1.24 ($P < 0.05$). It would only be necessary to add a single trial with a total of 380 patients randomised, with survival rates of 47.3% in the chemotherapy arm and 34.2% in the control arm, to convert this non-significant $z$-value to a significant one.

Cumulative meta-analyses, and the current study could be regarded as the third in a sequence for head and neck cancer, can be useful for the prompt detection of therapeutic advances. Experience from trials of treatment for myocardial infarction showed that, although early overviews were negative, the accumulation of evidence eventually favoured active therapy (Antman et al., 1992; Lau et al., 1992).

The main disadvantage of the present analysis is that it is based upon the published literature rather than upon data from individual patients. This raises problems with the

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Figure 3

- Upper 95% confidence limit by the DerSimonian Laird method; Lower 95% confidence limit by the DerSimonian Laird method. a. Rate differences for neoadjuvant studies. b. Rate differences for studies of synchronous chemotherapy and radiotherapy. c. Rate differences for adjuvant chemotherapy with cisplatinum/5-fluorouracil.

Figure 4

Sensitivity analyses of bias in data presentation and extraction. The method for correcting for possible bias is described in the text. a. The rate difference method, with 95% confidence intervals (DerSimonian and Laird). b. The odds ratio method, with 95% confidence intervals (Peto).
The data on the effects of chemotherapy upon distant metastasis are conflicting. This partly reflects the fact that distant metastases are an uncommon cause of treatment failure in head and neck cancer. The majority of patients who die do so from local regional failure. The inability of chemotherapy to prevent distant metastasis may therefore be more apparent than real.

An overview has two main purposes: firstly to suggest what, on the basis of data from clinical trials, might be defined as reasonable current practice; secondly, to provide a stimulus to further studies. Primary treatment with chemotherapy may provide useful relief of symptoms in patients treated palliatively, but there is little justification for the routine use of neoadjuvant chemotherapy in head and neck cancer. The claim, from the Veterans Administration study (The Department of Veterans Affairs Laryngeal Cancer Study Group, 1991), that neoadjuvant chemotherapy offers the possibility of avoiding mutilating surgery in head and neck cancer is controversial since that study, by virtue of its design, was unable to provide any evidence that chemotherapy plus radiotherapy was any better than radiotherapy alone

The data presented here suggest that we might put less effort into neoadjuvant studies and return to a more detailed investigation of the effectiveness of single-agent chemotherapy given synchronously with radiotherapy. Such treatment is simple and inexpensive. The survival benefit may be genuine: the next questions are what are the costs of such benefit in terms of excess morbidity and which is the best drug to use? Future trials will need to collect adequate data, both objective and subjective, on the toxicity of treatment. Radiation dose may also be important. It is essential that trials of synchronous chemotherapy report the radiation doses actually given, not simply those that were intended. If synchronous chemotherapy increases acute morbidity and necessitates the attenuation or curtailment of radiation therapy, then there may be little overall gain. Trials designed to answer these important questions need not be complex, nor should their entry criteria be too restrictive. Large simple studies are now required (Peto and Easton, 1989) to define more precisely the contribution of synchronous chemotherapy to the radiotherapeutic management of head and neck cancer.

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Appendix: List of trials analysed with reference numbers

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