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

AJ Munro

Department of Radiotherapy, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK.

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 Browman, 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 database; 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 extracting 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

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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 $60 - (0.05 \times 60) = 60 - 3 = 57$
control group $40 + (0.05 \times 40) = 40 + 2 = 42$

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 $>50\%$.

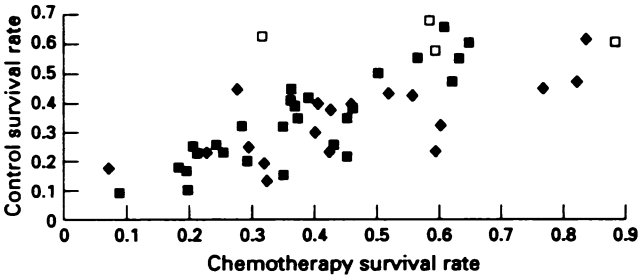

Figure 1 Scatter plot of event rates for the comparisons of survival data: neoad, (■) neoadjuvant studies; post, (□) chemotherapy given after definitive therapy; synch (◆) chemotherapy given synchronously with radiotherapy.

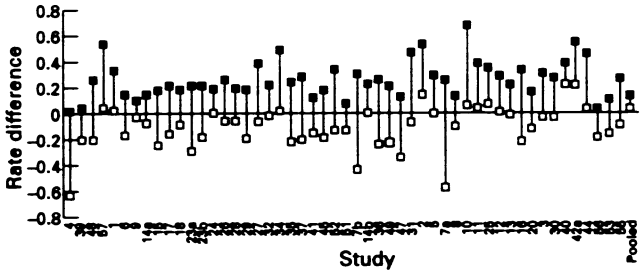

Figure 2 The rate differences for the 51 comparisons of survival data. Study numbers are the reference numbers for each trial (see Appendix). ■, upper 95% confidence limit by the DerSimonian Laird method; □, lower 95% confidence limit by the DerSimonian Laird method.

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 available from 43 comparisons and 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-

Table I Summary of trials analysed

Ref.	*Eligibility*	*Treatment in experimental group*	*Treatment in control group*	*ne*	*nc*	*surv t*	*es*	*cs*
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 @ 1.7 Gy pf 5f pw max 65 74	39	45	24 months	30	20
3	O Op N H L SCC t2 n2–3 t3 n1–3 t4 n0–3 m0	vcr/adr/bleo/mtx/5fu/ohurea/6mp then xrt(d7) then chemo during split then chemo x1 after xrt	32.5 Gy/13f rest 3w32.5 Gy 13f	30	28	12 months	6	2
4	t3nx mo oral cavity	mtx bleo vcr post surgery	xrt post surgery	16	16	36 months	5	10
5	adv III & IV hn scc fit for cur xrt O Op L H	5fu (1)-(3) first and 3rd week of xrt	xrt 66 Gy/33f/6.5w + saline placebo as for 5fu schedule	88	87	36 months	49/60	37/49
6	III IV O Op L II H	plat (1–4) bleo (1–4) vindesine(1) MMC (1) methpred (1–4) q21 then 2/52 then xrt	50–55 Gy at 1.8 Gy pf to 2 then assess: 65–75 Gy otherwise srg	48	52	42 months	10	12
7a	adv scc hn	6mp + xrt	xrt alone	11	9	12 months	3	4
7b	adv scc hn	ia mtx + FA	xrt alone	25	9	12 months	9	4
8	scc Op > = T2 or any infiltrative M0	xrt + bleo iv or im x2 pw for 5w	xrt 70 Gy in 7–8.5w	107	92	60 months	24	21
9	scc local t1–4n0–n3 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 scc pharynx	5fu (1–5) xrt 2 Gy pf (5–8) 5fu x2 pw during xrt to toxicity xrt total 60/30/6	60–75 Gy/30–37f/6–7w	17	15	12 months	14	7
11	inop III IV	bleo x2 pw during xrt then maint bleo + mtx q7d x16w	xrt 70 Gy at 1.8 Gy pf 5f pw	52	52	36 months	22	12
25	subset of O Op from above updated	xrt + 5fu (1–4) then x3 pw during xrt (6–7w) 5fu stopped if toxicity	60–70 Gy in 6–7w	68	68	60 months	22	9
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	60–70 Gy in 6–7w	76	79	12–108 months	24	15
13	scc m0 < 75 T2–3O T2–4OP T3–4L AII H,N,Antrum	mtx (0 & 14) + xrt 40–55 Gy in 15–16f in 3w	xrt alone	156	157	8–79 months	81	68
14a	untreated resectable II H II IV OOpH L	induction plat (1) bleo (3–7)	surgery + post op xrt 50 Gy 5w or 60 Gy 6w (residual disease)	140	152	60 months	52	53
14b	untreated resectable II H II IV OOpH L	as above induction then s + 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 Op N nose H (not St III tonsil or t3 L) m0	bleo (1–4) cyclo (1–5) mtx (1)+(5) 5fu (1–5) x2 q21 then standard Rx	preop xrt + srg or xrt ± node dissection	39	39	24 months	14	16
16	adv scc hn	xrt 45 Gy in 4.5 w to 75 Gy in 9.5 w + oh urea mon wed fri during xrt	xrt alone	24	16	24 months	7	4
17	Op H L O t3,4 t2 H	plat (1–3) 5fu (1–5) vindesine (1&5) then 3w then xrt	xrt 55 Gy then assess if > 50% regr then to 70 Gy otherwise srg	55	53	36 months	31	29
18	pyriform fossa t2 t3 n0 n1 n3 resectable	vcr (1) bleo (1) mtx (1&2) then surgery then xrt 65 Gy	srg + xrt only	89	98	60 months	31	31
19	operable scc preop EOL	bleo x3 pw 1hr before xrt	30 Gy 5w 15pf split (wk 3 rest)	15	14	24 months	14	7
20	L t3t4 or t1–4n + H t1–3 n0–3	MMC (1&43) 5fu (1–4) (43–46) xrt 25 Gy 10f 2w (1–14) 25 Gy 10f 2w (43–57)	xrt 25 Gy/10f/2w–4w gap 25 Gy/10f/2w	104	105	60 months	42	42
21	adv scc	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	1–12 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 45d)	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 (1–5) then xrt	xrt 60–66 Gy in 6–6.5w at 10 Gy pw	28	28	36 months	5	5
24	resectable SCC III–IV L O Op II III IV H	plat (1) 5fu (1–5) q21 [x3] then xrt	xrt (low risk) 50–54 Gy @ 1.8 Gy pf (high risk) 60 Gy @ 1.8 Gy pf	222	224	48 months	102	85
26	scc any t n3 t3,t4 any n	mtx (1) ((4) (9) (12) (15)) then xrt (ave 63.6 Gy)	xrt ± srg xrt dose ave 64.2 Gy	36	39	36 months	7	4
28	scc O Op H L	carbo(1) 5fu(1–5) q21 x3 then xrt +/– srg	srg + xrt xrt alone if cr to chemo	108	110	24 months	70	66
29	scc O Op	bleo (1–5) mtx (2) 5fu (2) plat (4) x3	srg + xrt or xrt alone	54	53	24 months	21	22
27	I II III IV O Op H II III IV L	plat (1) 5fu (1–5) q21 x3 (nr switch after 2) then local rx	xrt 70 Gy/1.8 Gy pf/8w or srg + postop xrt	37	38	24 months	23	18

Table 1 Summary of trials analysed

Ref.	*Eligibility*	*Treatment in experimental group*	*Treatment in control group*	*ne*	*nc*	*surv t*	*es*	*cs*
30	unresectable III IV scc < 76 Op H O L	plat (1–5) 5fu (1–5) q21 20 GY xrt x3 ie c-xrt-c-xrt-c-xrt-c	70 Gy (a) 1.8 Gy to 2 Gy pf	80	77	36 months	32	23
31	O Op N H L t2 t3 t4	chemo then xrt 15–19 24/10/10d then chemo 29 then xrt 43–47(24/10) then chemo 57 onwards	2f/day 24 Gy/10f/10d then 24d then 24 Gy/10f/10d	23	13	12 months	8	2
32	St III and IV	plat (1) 5fu (1–5) q21 x4 then Irt	Irt: srg + 60 Gy (op) xrt 65 Gy (inop)	118	119	36 months	34	24
34	t3–4nx to tx n2–3 primary or recurrent scc O Op	plat (1) mtx (2&5) bleo (2–5) xrt 20/10 (14–28) chemo 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
35	scc IV unresectable male m0	vcr + mtx + FA q 21d x2 then xrt	xrt 70 Gy/7w	12	11	24 months	1	1
36	resectable curable scc hn excl sal	mtx escalating wkly x4 then s(not N) thenmtx q7dx4 then xrt then mtx q7 x8 (np xrt mtx x12)	srg(not N) + xrt 60–65 Gy at 1.8 to 2 Gy pf	32	28	40 months	16	14
37	O (tongue, floor of mouth, soft pal, rmt, buccal mucosa)	mtx ia stop at tox 2w 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
38	ca hn O 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
39	N SCC m0	if cr or good pr to xrt ass at 65d vcr (1) cyclo(1–4) adr (1) q28 x12 (planned but revised to 6)	xrt 60–70 Gy at 1.8 to 2 Gy pf 5f pw	113	116	48 months	66	78
40	t3–t4 n0–n3 mo scc	xrt 60/2/6 synchr 5 fu every 2d iv ie x21	xrt 60 Gy/2 Gy pf/6w	300	277	60 months	180	89
41	st III IV O Op L H	plat (1) mtx (1) bleo (1&8) vcr (1) q21x3 then srg day 84 (s + post op xrt)	surgery then xrt	82	76	60 months	23	24
42a	O t3 t4 n0–2 scc buccal mo	bleo x3 pw during xrt 55–60 in 7w 3f pw (bleo 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
42b	O t3 t4 n0–2 scc buccal mo	bleo q 4d x4 then xrt + bleo 3 x1	xrt 55–60 Gy 3f pw (2.85 to 3.05 Gy pf) 7w	20	20	n/s	n/s	n/s
43a	Op(tongue base)	vcr bleo mtx mmc 5fu x2 then xrt	xrt	23	19	n/s	n/s	n/s
43b	Op (tongue base)	xrt + syn bleo	xrt	19	19	n/s	n/s	n/s
44	max sinus	conv xrt + ia 5fu	conv xrt	25	38	12 months	21	23
45	st III IV scc t3 or t4 O Op H L tx N	vcr ohcort + mtx 5fu + ohc ohurea 6mp cyclo iv xrt (28) q21d x12	xrt only 40–60 Gy in 3–6w	46	39	60 months	11	10
56	scc not t1 L	xrt + Ohurea x2 pw	6–10 Gy 5–6f pw 8–12w	75	75	60 months	5	13
47	L t4 or n3 H all t3,4 or n3 adv O Op N E	vbl/bleo/mtx/cyclo/5fu x2 then xrt/srg then chemo x6	xrt = /– srg alone	33	35	24 months	13	18
48	scc ant tongue floor of mouth	mtx q28 iv inf with FA + bleo pw im 2yrs mtx bleo given after defin rx	defin rx only	32	33	48 months	19	19
49	st II St III poor prog scc hn	mtx im(1) (5) (9) then 2/52 then Ir then 6w then adj mtx or plat/adr	xrt (> 65 Gy (a) 2 Gy pf in 6.5w) or xrt choice made before rand	41	41	60 months	15	16
50	St III & IV	mtx po plat (2) q 7d x???? post srg/xrt	srg/xrt	12	26	n/s	n/s	n/s
52	III, IV O Op N S L H St II pyriform sinus m0	plat (1) 5fu (1–5) q21 x2–x3 then conv rx	xrt alone 70 Gy 2 Gy pf 7w or preop xrt 50 Gy (a) 2 Gy pf in 5w	30	33	24 months	19	18
51	III IV scc L	plat (1) 5fu(1–5) q21 x2 to x3 depending upon resp > = PR to xrt 66–76 Gy 1.8–2.0 Gy	surg + 50–60 Gy depending upon margins	166	166	48 months	101	108
53	scc hn II–IV m0 O Op N H L S	bleo im 1hr before each frac xrt until toxicity		111	111	60 months	42	47
54a	buccal mucosa t3 t4 m0	5Fu iv (1–5) xrt starts day 10–15	xrt alone 65 Gy in 6–7w	24	22	n/s	n/s	n/s
54b	buccal mucosa t3 t4 m0	iudr iv (1–5) xrt starts day 10–15	xrt only 65 Gy in 6w	21	22	n/s	n/s	n/s
54c	buccal mucosa t3 t4 m0	mtx iv (1–5) xrt starts day 10–15	xrt only 65 Gy in 6w	20	22	n/s	n/s	n/s
55	scc O Op L H N t1n2,3 t2 n2, t3 t4	mitomycin c on day 5 of xrt (adv pts further post xrt at 6w) xrt 56 to 67.7 at 2pf	xrt only 65 Gy in 6w xrt alone 59–67.65 Gy	59	61	60 months	27	24

Abbreviations: ne, number of patients in experimental group; nc, number of patients in control group; surv t, time at which survival assessment was made; es, number of survivors in experimental group; cs, number of survivors in control group; ca, carcinoma; scc, squamous cell carcinoma; hn, 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; regr, regression; nr, no response; cr, complete response; pr, partial response; defin, 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, methotrexate; carbo, carboplatin; plat, cisplatinum; 5fu, 5 fluorouracil; OHcort, hydrocortisone; adr, doxorubicin; OHurea hydroxyurea; bleo, bleomycin; cyclo, cyclophosphamide; 6mp, 6 mercaptopurine; methpred, methylprednisolone; FA, folinic acid; vcr, vincristine.

Table II Summary of survival data for the 51 comparisons

Trial	Type	No. of pts	Rate diff.	RD low	RD high	Odds ratio	OR low	OR high	Chi sq	P for sig.	PFN
1	p	142	**0.17**	0.02	0.33	**2.14**	1.07	4.27	4.69	**0.030**	
4	p	32	**−0.31**	−0.64	0.02	**0.30**	0.08	1.16	3.04	**0.081**	0.021
39	p	229	**−0.09**	−0.21	0.04	**0.69**	0.40	1.17	1.91	**0.167**	0.007
48	p	65	**0.02**	−0.22	0.26	**1.08**	0.40	2.86	0.02	**0.884**	0.468
57	p	46	**0.28**	0.04	0.53	**4.62**	1.20	17.85	4.92	**0.026**	
6	n	100	**−0.02**	−0.18	0.14	**0.88**	0.34	2.25	0.07	**0.788**	0.005
9	n	638	**0.02**	−0.04	0.09	**1.13**	0.79	1.63	0.47	**0.495**	<.001
15	n	78	**−0.05**	−0.27	0.16	**0.81**	0.33	2.00	0.21	**0.644**	0.067
17	n	108	**0.02**	−0.17	0.20	**1.07**	0.50	2.27	0.03	**0.864**	0.309
18	n	187	**0.03**	−0.10	0.17	**1.15**	0.63	2.12	0.21	**0.644**	0.040
24	n	446	**0.08**	−0.01	0.17	**1.39**	0.95	2.02	2.92	**0.087**	0.103
26	n	75	**0.09**	−0.07	0.25	**2.06**	0.58	7.36	1.25	**0.264**	0.024
27	n	75	**0.15**	−0.07	0.37	**1.80**	0.73	4.45	1.63	**0.201**	0.886
28	n	218	**0.05**	−0.08	0.18	**1.23**	0.71	2.12	0.54	**0.464**	0.426
29	n	107	**−0.03**	−0.21	0.16	**0.90**	0.42	1.94	0.08	**0.783**	0.065
31	n	36	**0.19**	−0.08	0.47	**2.56**	0.57	11.44	1.51	**0.218**	0.895
32	n	237	**0.09**	−0.02	0.20	**1.59**	0.88	2.88	2.39	**0.122**	0.030
34	n	59	**0.24**	0.01	0.47	**2.83**	0.97	8.26	3.64	**0.057**	0.730
35	n	23	**−0.01**	−0.24	0.22	**0.91**	0.05	15.62	0.00	**0.950**	0.045
36	n	60	**0.00**	−0.25	0.25	**1.00**	0.37	2.73	0.00	**1.000**	0.330
37	n	39	**0.02**	−0.22	0.26	**1.17**	0.23	5.91	0.04	**0.849**	0.058
41	n	158	**−0.04**	−0.18	0.11	**0.85**	0.43	1.67	0.23	**0.629**	0.003
45	n	85	**−0.02**	−0.20	0.17	**0.91**	0.34	2.44	0.03	**0.855**	0.018
47	n	68	**−0.12**	−0.35	0.11	**0.62**	0.24	1.60	0.97	**0.320**	0.040
49	n	82	**−0.02**	−0.23	0.19	**0.90**	0.37	2.19	0.05	**0.821**	0.093
51	n	332	**−0.04**	−0.15	0.06	**0.84**	0.54	1.30	0.63	**0.427**	0.014
52	n	63	**0.09**	−0.15	0.33	**1.43**	0.53	3.87	0.49	**0.483**	0.834
14a	n	292	**0.02**	−0.09	0.13	**1.10**	0.68	1.78	0.16	**0.686**	0.011
14b	n	303	**0.10**	−0.01	0.21	**1.53**	0.96	2.41	3.25	**0.071**	0.269
23a	n	40	**−0.05**	−0.31	0.21	**0.76**	0.17	3.27	0.14	**0.708**	0.052
23b	n	56	**0.00**	−0.20	0.20	**1.00**	0.26	3.88	0.00	**1.000**	0.017
7b	n	34	**−0.08**	−0.46	0.29	**0.71**	0.15	3.31	0.19	**0.660**	0.211
2	s	84	**0.32**	0.13	0.52	**3.79**	1.59	9.03	9.04	**0.003**	
3	s	58	**0.13**	−0.04	0.30	**2.89**	0.66	12.72	1.97	**0.150**	0.020
5	s	175	**0.13**	−0.02	0.28	**1.69**	0.93	3.05	3.01	**0.083**	0.871
8	s	199	**0.00**	−0.12	0.11	**0.98**	0.50	1.90	0.00	**0.947**	0.000
10	s	32	**0.36**	0.05	0.67	**4.63**	1.10	19.52	4.36	**0.037**	
11	s	104	**0.19**	0.02	0.37	**2.38**	1.05	5.37	4.33	**0.037**	
12	s	155	**0.13**	−0.01	0.26	**1.94**	0.94	4.01	3.24	**0.072**	0.242
13	s	313	**0.09**	−0.02	0.20	**1.41**	0.91	2.20	2.32	**0.128**	0.320
16	s	40	**0.04**	−0.24	0.32	**1.23**	0.30	4.97	0.08	**0.775**	0.262
20	s	209	**0.00**	−0.13	0.14	**1.02**	0.59	1.76	0.00	**0.955**	0.029
25	s	136	**0.19**	0.05	0.33	**2.94**	1.32	6.53	7.01	**0.008**	
30	s	157	**0.10**	−0.05	0.25	**1.56**	0.81	2.99	1.76	**0.185**	0.318
40	s	577	**0.28**	0.20	0.36	**3.06**	2.21	4.24	44.87	**<.001**	
44	s	63	**0.23**	0.02	0.45	**2.99**	1.01	8.92	3.88	**0.049**	
53	s	222	**0.05**	−0.08	0.17	**1.21**	0.71	2.06	0.47	**0.494**	0.089
55	s	120	**0.06**	−0.11	0.24	**1.30**	0.63	2.67	0.50	**0.479**	0.327
56	s	150	**−0.11**	−0.21	0.00	**0.37**	0.14	0.98	4.01	**0.045**	
42a	s	116	**0.36**	0.20	0.53	**4.34**	2.08	9.05	15.28	**<.001**	
7a	s	20	**−0.17**	−0.59	0.25	**0.49**	0.08	2.95	0.61	**0.435**	0.137

RD, rate difference; OR, Odds ratio; low, high, 95% confidence limits; Chi sq, χ^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 (locoregional 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	0.93	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	4141	**3.7**	0.9	6.5	**1.2**	1.04	1.35	6.4	0.011	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 χ^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.

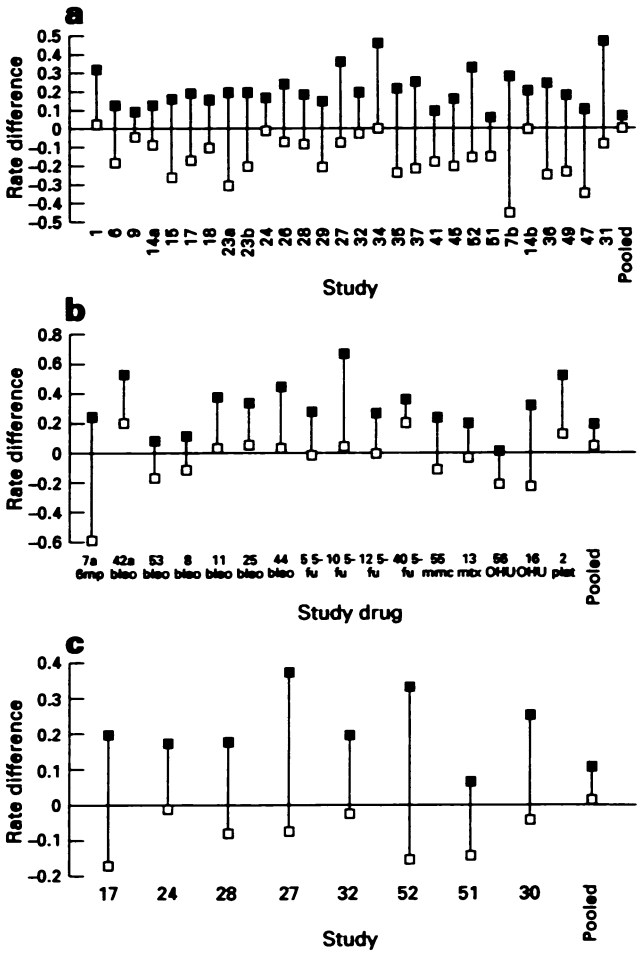

Figure 3 ■, Upper 95% confidence limit by the DerSimonian Laird method; □, lower 95% confidence limit by the DerSimonian Laird method. **a**, Rate differences for neoadjuvant studies. **b**, Rate differences for studies of synchronous chemotherapy and radiotherapy. **c**, Rate differences for adjuvant chemotherapy with cisplatinum/5-fluorouracil.

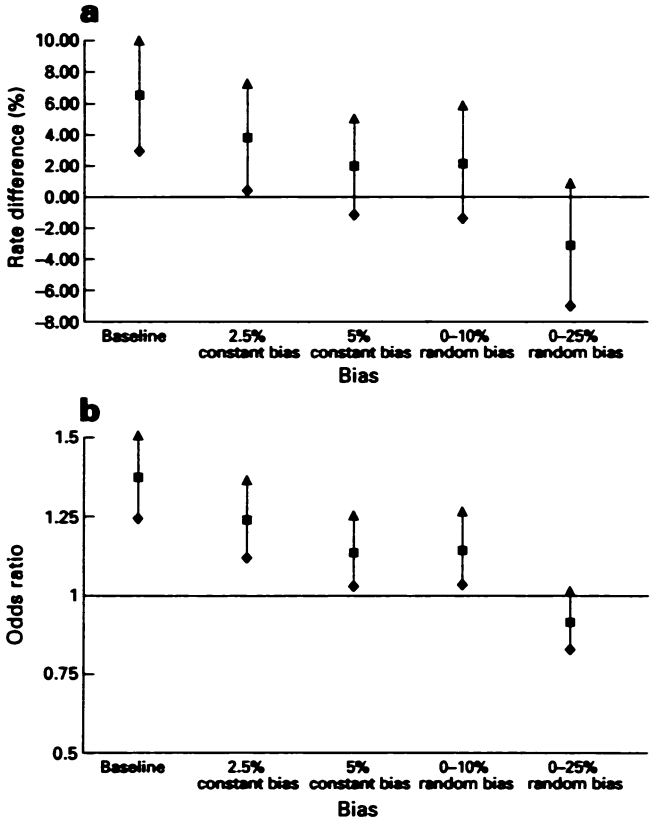

Figure 4 Sensitivity analyses of bias in data presentation and extraction. The method for correcting for possible bias is described in the text. **a**, The rate difference method, with 95% confidence intervals (DerSimonian and Laird). **b**, The odds ratio method, with 95% confidence intervals (Peto).

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 χ^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 χ^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: 51 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

assessment of event rates (Stewart and Parmar, 1993). The inability to use a constant time point for survival, for example, introduces potentially serious bias since the survival at arbitrary time points does not, and cannot, represent the overall shape of the survival curve. The sensitivity analyses clearly show that the overall conclusion of this overview is sensitive to this type of bias. The only solution is to perform a per-patient analysis, and such a study is currently under way (MKB Parmar, 1994, personal communication). Unfortunately, it will be at least 2 years until the results are published; in the meantime literature-based analysis, with all its imperfections, will have to suffice.

The present overview suggests that the largest gains, in terms of survival, may be obtained by using chemotherapy synchronously with radiotherapy. The demonstration that gains from neoadjuvant therapy are relatively modest compared with the benefits from synchronous therapy is provocative and, if true, would require an explanation consistent with the basic biology of squamous carcinoma of the head and neck. Squamous carcinomas of the head and neck have high cell loss factors: 90% of cells produced by mitosis of clonogenic cells may be lost through exfoliation and migration. Relatively modest killing of clonogens will, through the effects of cell loss, produce rapid shrinkage of tumour. This rapid regression, is, however, virtually an epiphenomenon – albeit a gratifying one.

The ultimate outcome is dictated by those clonogenic cells which are not lost and, in particular, their resistance to therapy. Because of cell loss, a clinically apparent tumour is genetically old, a 2 cm squamous cell carcinoma of the head and neck is perhaps 600–1000 generations old. In the absence of cell loss it would take only 30–40 generations to reach this size. The chance of a mutation emerging that confers drug resistance increases with each generation. There is a high probability that, at diagnosis, even small tumours of the head and neck will contain clonogenic cells which are, *de novo*, resistant to cytotoxic drugs. Cell loss can therefore explain both the initial responsiveness and the ultimate resistance to chemotherapy of these tumours.

Accelerated repopulation of clonogenic cells in tumours may compromise the effectiveness of radiotherapy for head and neck cancers (Withers *et al.*, 1988). Neoadjuvant chemotherapy, by providing the stimulus for such repopulation several weeks before the start of radiotherapy, might exacerbate this problem. With synchronous chemotherapy, the problem of such treatment-induced perturbations does not apply.

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 attentuation 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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7a synchronous chemotherapy
7b neoadjuvant chemotherapy

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14a neoadjuvant *vs* standard therapy
14b neoadjuvant + maintenance *vs* standard therapy

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23b low-dose methotrexate

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