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Chemotherapy, radiotherapy and combined modality for Hodgkin's disease, with emphasis on second cancer risk (Review)

Franklin J, Paus MD, Pluetschow A, Specht L

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Chemotherapy, radiotherapy and combined modality for Hodgkin's disease, with emphasis on second cancer risk (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	6
Figure 1.	8
Figure 2.	9
Figure 3.	10
Figure 4.	11
Figure 5.	12
Figure 6.	12
Figure 7.	13
Figure 8.	13
Figure 9.	14
Figure 10.	15
Figure 11.	15
Figure 12.	16
Figure 13.	17
Figure 14.	18
Figure 15.	19
Figure 16.	20
Figure 17.	21
Figure 18.	22
Figure 19.	23
Figure 20.	24
Figure 21.	25
Figure 22.	26
Figure 23.	26
Figure 24.	27
Figure 25.	28
Figure 26.	28
Figure 27.	29
Figure 28.	29
Figure 29.	30
Figure 30.	30
Figure 31.	31
Figure 32.	32
Figure 33.	33
Figure 34.	34
Figure 35.	34
Figure 36.	35
Figure 37.	35
Figure 38.	36
DISCUSSION	36
AUTHORS' CONCLUSIONS	38
ACKNOWLEDGEMENTS	40
REFERENCES	41
CHARACTERISTICS OF STUDIES	51
DATA AND ANALYSES	67

Analysis 1.1. Comparison 1 RT vs. CT, Outcome 1 overall survival.	68
Analysis 1.2. Comparison 1 RT vs. CT, Outcome 2 OS - early stages - sex.	69
Analysis 1.3. Comparison 1 RT vs. CT, Outcome 3 OS - advanced stages - sex.	69
Analysis 1.4. Comparison 1 RT vs. CT, Outcome 4 progression free survival.	70
Analysis 1.5. Comparison 1 RT vs. CT, Outcome 5 PFS - censored at cut-off date.	70
Analysis 1.6. Comparison 1 RT vs. CT, Outcome 6 PFS - early stages - sex.	71
Analysis 1.7. Comparison 1 RT vs. CT, Outcome 7 PFS - advanced stages - sex.	71
Analysis 1.8. Comparison 1 RT vs. CT, Outcome 8 second malignancy free survival.	72
Analysis 1.9. Comparison 1 RT vs. CT, Outcome 9 SM before progression/relapse.	73
Analysis 1.10. Comparison 1 RT vs. CT, Outcome 10 SM free survival - early stages - sex.	73
Analysis 1.11. Comparison 1 RT vs. CT, Outcome 11 SM free survival - advanced stages - sex.	74
Analysis 2.1. Comparison 2 CT v CRT, Outcome 1 overall survival.	79
Analysis 2.2. Comparison 2 CT v CRT, Outcome 2 OS - unconfounded trials.	79
Analysis 2.3. Comparison 2 CT v CRT, Outcome 3 OS - early stages - sex.	80
Analysis 2.4. Comparison 2 CT v CRT, Outcome 4 OS - advanced stages - sex.	81
Analysis 2.5. Comparison 2 CT v CRT, Outcome 5 OS- early stages - age.	82
Analysis 2.6. Comparison 2 CT v CRT, Outcome 6 OS - advanced stages - age.	82
Analysis 2.7. Comparison 2 CT v CRT, Outcome 7 OS - early stages - type of RT.	84
Analysis 2.8. Comparison 2 CT v CRT, Outcome 8 OS - advanced stages - type of RT.	85
Analysis 2.9. Comparison 2 CT v CRT, Outcome 9 PFS confounded advanced.	85
Analysis 2.10. Comparison 2 CT v CRT, Outcome 10 progression free survival.	86
Analysis 2.11. Comparison 2 CT v CRT, Outcome 11 PFS - censored at cut-off date.	87
Analysis 2.12. Comparison 2 CT v CRT, Outcome 12 PFS - unconfounded trials only.	87
Analysis 2.13. Comparison 2 CT v CRT, Outcome 13 PFS - early stages - sex.	88
Analysis 2.14. Comparison 2 CT v CRT, Outcome 14 PFS - advanced stages - sex.	89
Analysis 2.15. Comparison 2 CT v CRT, Outcome 15 PFS - early stages - age.	90
Analysis 2.16. Comparison 2 CT v CRT, Outcome 16 PFS - advanced stages - age.	91
Analysis 2.17. Comparison 2 CT v CRT, Outcome 17 second malignancy free survival.	92
Analysis 2.18. Comparison 2 CT v CRT, Outcome 18 SM free survival - censored at cut-off date.	93
Analysis 2.19. Comparison 2 CT v CRT, Outcome 19 SM free survival - unconfounded trials only.	94
Analysis 2.20. Comparison 2 CT v CRT, Outcome 20 SM free survival - confounded trials only.	94
Analysis 2.21. Comparison 2 CT v CRT, Outcome 21 SM before progression or relapse.	95
Analysis 2.22. Comparison 2 CT v CRT, Outcome 22 SM free survival - early stages - sex.	96
Analysis 2.23. Comparison 2 CT v CRT, Outcome 23 SM free survival - advanced stages - sex.	96
Analysis 2.24. Comparison 2 CT v CRT, Outcome 24 SM free survival - early stages - age.	97
Analysis 2.25. Comparison 2 CT v CRT, Outcome 25 SM free survival - advanced stages - age.	98
Analysis 2.26. Comparison 2 CT v CRT, Outcome 26 SM free survival - non-malignant skin cancers excluded.	100
Analysis 2.27. Comparison 2 CT v CRT, Outcome 27 SM before progression/relapse - non-malignant skin cancers excluded.	100
Analysis 2.28. Comparison 2 CT v CRT, Outcome 28 solid tumors.	101
Analysis 2.29. Comparison 2 CT v CRT, Outcome 29 solid tumors - non-malignant skin cancers excluded.	102
Analysis 2.30. Comparison 2 CT v CRT, Outcome 30 solid tumors before progression/relapse.	103
Analysis 2.31. Comparison 2 CT v CRT, Outcome 31 lung cancers.	104
Analysis 2.32. Comparison 2 CT v CRT, Outcome 32 breast cancers.	104
Analysis 2.33. Comparison 2 CT v CRT, Outcome 33 AML/MDS.	105
Analysis 2.34. Comparison 2 CT v CRT, Outcome 34 AML/MDS before progression/relapse.	106
Analysis 2.35. Comparison 2 CT v CRT, Outcome 35 NHL.	106
Analysis 2.36. Comparison 2 CT v CRT, Outcome 36 NHL before progression/relapse.	107
Analysis 3.1. Comparison 3 RT v CRT, Outcome 1 overall survival.	112
Analysis 3.2. Comparison 3 RT v CRT, Outcome 2 OS - early stages - sex.	113
Analysis 3.3. Comparison 3 RT v CRT, Outcome 3 OS - advanced stages - sex.	114
Analysis 3.4. Comparison 3 RT v CRT, Outcome 4 OS - early stages - age.	114
Analysis 3.5. Comparison 3 RT v CRT, Outcome 5 OS - advanced stages - age.	116

Analysis 3.6. Comparison 3 RT v CRT, Outcome 6 OS - unconfounded trials only.	116
Analysis 3.7. Comparison 3 RT v CRT, Outcome 7 progression free survival.	117
Analysis 3.8. Comparison 3 RT v CRT, Outcome 8 PFS - early stages - sex.	118
Analysis 3.9. Comparison 3 RT v CRT, Outcome 9 PFS - advanced stages - sex.	119
Analysis 3.10. Comparison 3 RT v CRT, Outcome 10 PFS - early stages - age.	119
Analysis 3.11. Comparison 3 RT v CRT, Outcome 11 PFS - advanced stages - age.	121
Analysis 3.12. Comparison 3 RT v CRT, Outcome 12 PFS - censored at cut-off date.	122
Analysis 3.13. Comparison 3 RT v CRT, Outcome 13 PFS - unconfounded trials only.	122
Analysis 3.14. Comparison 3 RT v CRT, Outcome 14 second malignancy free survival.	123
Analysis 3.15. Comparison 3 RT v CRT, Outcome 15 SM free survival - censored at cut-off date.	124
Analysis 3.16. Comparison 3 RT v CRT, Outcome 16 SM free survival - unconfounded trials only.	125
Analysis 3.17. Comparison 3 RT v CRT, Outcome 17 SM free survival - confounded trials only.	125
Analysis 3.18. Comparison 3 RT v CRT, Outcome 18 SM before progression/relapse.	126
Analysis 3.19. Comparison 3 RT v CRT, Outcome 19 SM free survival - early stages - sex.	127
Analysis 3.20. Comparison 3 RT v CRT, Outcome 20 SM free survival - advanced stages - sex.	128
Analysis 3.21. Comparison 3 RT v CRT, Outcome 21 SM free survival - early stages - age.	128
Analysis 3.22. Comparison 3 RT v CRT, Outcome 22 SM free survival - advanced stages - age.	130
Analysis 3.23. Comparison 3 RT v CRT, Outcome 23 SM free survival - subgroup +/- mustargen.	130
Analysis 3.24. Comparison 3 RT v CRT, Outcome 24 SM free survival - non-malignant skin cancers excluded.	131
Analysis 3.25. Comparison 3 RT v CRT, Outcome 25 SM before progression/relapse - non-malignant skin cancers excluded.	132
Analysis 3.26. Comparison 3 RT v CRT, Outcome 26 solid tumors.	133
Analysis 3.27. Comparison 3 RT v CRT, Outcome 27 solid tumors - non-malignant skin cancers excluded.	133
Analysis 3.28. Comparison 3 RT v CRT, Outcome 28 solid tumors before progression/relapse.	134
Analysis 3.29. Comparison 3 RT v CRT, Outcome 29 lung cancers.	135
Analysis 3.30. Comparison 3 RT v CRT, Outcome 30 lung cancers before prog/rel.	136
Analysis 3.31. Comparison 3 RT v CRT, Outcome 31 breast cancers.	136
Analysis 3.32. Comparison 3 RT v CRT, Outcome 32 AML/MDS - early stages only.	137
Analysis 3.33. Comparison 3 RT v CRT, Outcome 33 AML/MDS before progression/relapse.	137
Analysis 3.34. Comparison 3 RT v CRT, Outcome 34 NHL - early stages only.	138
Analysis 3.35. Comparison 3 RT v CRT, Outcome 35 NHL before progression/relapse.	138
Analysis 4.1. Comparison 4 IF-RT vs. EF-RT, Outcome 1 overall survival.	143
Analysis 4.2. Comparison 4 IF-RT vs. EF-RT, Outcome 2 OS - RT plus CT.	144
Analysis 4.3. Comparison 4 IF-RT vs. EF-RT, Outcome 3 OS - RT without CT.	145
Analysis 4.4. Comparison 4 IF-RT vs. EF-RT, Outcome 4 OS - early stages - sex.	145
Analysis 4.5. Comparison 4 IF-RT vs. EF-RT, Outcome 5 OS - advanced stages - sex.	146
Analysis 4.6. Comparison 4 IF-RT vs. EF-RT, Outcome 6 OS - early stages - age.	146
Analysis 4.7. Comparison 4 IF-RT vs. EF-RT, Outcome 7 OS - advanced stages - age.	148
Analysis 4.8. Comparison 4 IF-RT vs. EF-RT, Outcome 8 progression free survival.	148
Analysis 4.9. Comparison 4 IF-RT vs. EF-RT, Outcome 9 PFS - censored at cut-off date.	149
Analysis 4.10. Comparison 4 IF-RT vs. EF-RT, Outcome 10 PFS - RT plus CT.	150
Analysis 4.11. Comparison 4 IF-RT vs. EF-RT, Outcome 11 PFS - RT without CT.	150
Analysis 4.12. Comparison 4 IF-RT vs. EF-RT, Outcome 12 PFS - early stages - sex.	151
Analysis 4.13. Comparison 4 IF-RT vs. EF-RT, Outcome 13 PFS - advanced stages - sex.	152
Analysis 4.14. Comparison 4 IF-RT vs. EF-RT, Outcome 14 PFS - early stages - age.	152
Analysis 4.15. Comparison 4 IF-RT vs. EF-RT, Outcome 15 PFS - advanced stages - age.	154
Analysis 4.16. Comparison 4 IF-RT vs. EF-RT, Outcome 16 second malignancy free survival.	154
Analysis 4.17. Comparison 4 IF-RT vs. EF-RT, Outcome 17 SM free survival - censored at cut-off date.	155
Analysis 4.18. Comparison 4 IF-RT vs. EF-RT, Outcome 18 SM free survival - RT plus CT.	156
Analysis 4.19. Comparison 4 IF-RT vs. EF-RT, Outcome 19 SM free survival - RT without CT.	156
Analysis 4.20. Comparison 4 IF-RT vs. EF-RT, Outcome 20 SM before progression or relapse.	157
Analysis 4.21. Comparison 4 IF-RT vs. EF-RT, Outcome 21 SM free survival - early stages - sex.	157
Analysis 4.22. Comparison 4 IF-RT vs. EF-RT, Outcome 22 SM free survival - advanced stages - sex.	158

Analysis 4.23. Comparison 4 IF-RT vs. EF-RT, Outcome 23 SM free survival - early stages - age.	159
Analysis 4.24. Comparison 4 IF-RT vs. EF-RT, Outcome 24 SM free survival - advanced stages - age.	160
Analysis 4.25. Comparison 4 IF-RT vs. EF-RT, Outcome 25 SM free survival - non-malignant skin cancers excluded.	161
Analysis 4.26. Comparison 4 IF-RT vs. EF-RT, Outcome 26 SM before progression/relapse - non-malignant skin cancers excluded.	161
Analysis 4.27. Comparison 4 IF-RT vs. EF-RT, Outcome 27 solid tumors.	162
Analysis 4.28. Comparison 4 IF-RT vs. EF-RT, Outcome 28 solid tumors before progression/relapse.	163
Analysis 4.29. Comparison 4 IF-RT vs. EF-RT, Outcome 29 solid tumors - non-malignant skin cancers excluded.	164
Analysis 4.30. Comparison 4 IF-RT vs. EF-RT, Outcome 30 breast cancers.	164
Analysis 4.31. Comparison 4 IF-RT vs. EF-RT, Outcome 31 lung cancers.	165
Analysis 4.32. Comparison 4 IF-RT vs. EF-RT, Outcome 32 AML/MDS.	165
Analysis 4.33. Comparison 4 IF-RT vs. EF-RT, Outcome 33 NHL.	166
ADDITIONAL TABLES	167
WHAT'S NEW	178
CONTRIBUTIONS OF AUTHORS	178
DECLARATIONS OF INTEREST	178
SOURCES OF SUPPORT	178
INDEX TERMS	178

[Intervention Review]

Chemotherapy, radiotherapy and combined modality for Hodgkin's disease, with emphasis on second cancer risk

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ABSTRACT

Background

Second malignancies (SM) are a major late effect of treatment for Hodgkin's disease (HD). Reliable comparisons of SM risk between alternative treatment strategies are lacking.

Objectives

Radiotherapy (RT), chemotherapy (CT) and combined chemo-radiotherapy (CRT) for newly-diagnosed Hodgkin's disease are compared with respect to SM risk, overall (OS) and progression-free (PFS) survival. Further, involved-field (IF-)RT is compared to extended-field (EF-)RT.

Search methods

We searched the Cochrane Controlled Trials Register, PubMed, EMBASE, CancerLit, LILACS, relevant conference proceedings, trials lists and publications.

Selection criteria

RCTs accruing 30+ patients and completing accrual before/during 2000, comparing at least two treatment modalities for newly-diagnosed HD.

Data collection and analysis

Individual patient data were collected and assessed for data quality. Trialists submitted additional information concerning methods and data quality. Peto Odds Ratios (OR) with 95% confidence intervals (CI) were calculated for OS, PFS and SM-free survival. Secondary acute leukaemia (AL), non-Hodgkin's lymphoma (NHL) and solid tumours (ST) were also analysed separately.

Main results

37 trials (9312 patients) were analysed: 15 (3343) for RT vs. CRT, 16 (2861) for CT vs. CRT, 3 (415) for RT vs. CT and 10 (3221) for IF-RT vs. EF-RT. CRT was superior to RT in terms of OS (OR=0.76, 95% CI 0.66 to 0.89, $P = 0.0004$), PFS (OR=0.49, 95% CI 0.43 to 0.56, $P < 0.0001$) and SM (OR = 0.78, 95% CI 0.62 to 0.98, $P = 0.03$). The superiority of CRT also applied to early and advanced stages (mainly IIIA) separately. Excess SM with RT is due mainly to ST and is apparently caused by greater need for salvage therapy after RT.

CRT was superior to CT in terms of PFS (OR = 77, 95 % CI 0.68 to 0.77, $P < 0.0001$). OS was better with CRT for early stages only (OR=0.62, 95% CI 0.44 to 0.88, $P = 0.006$). SM risk was higher with CRT (OR = 1.38, 95% CI 1.00 to 1.89, $P = 0.05$), although not significant for early stages alone. This effect, also seen in AL and ST separately, was due directly to first-line treatment.

Data were insufficient to compare RT to CT.

EF-RT was superior to IF-RT (each additional to CT in most trials) in terms of PFS (OR=81, 95% CI 0.68 to 0.95, $P = 0.009$) but not OS. No significant difference in SM was observed.

Authors' conclusions

CRT seems to be optimal for most early stage (I-II) HD patients. For advanced stages (III to IV), CRT better prevents progression/relapse but CT alone seems to cause less SM.

RT alone gives a higher overall SM risk than CRT due to increased need for salvage therapy. Reduced SM risk after IF-RT instead of EF-RT could not be demonstrated. Due to the large number of studies excluded because no IPD were received, to the inclusion of many outdated treatments and to the limited amount of long-term data, one must be cautious in applying these results to current therapies.

PLAIN LANGUAGE SUMMARY

Second malignancy risk in Hodgkin's disease patients depends upon the choice of chemotherapy and/or radiotherapy as first-line treatment.

Hodgkin's disease (HD) patients are usually treated initially with radiotherapy alone (RT; early stages only), chemotherapy alone (CT) or combined chemo-radiotherapy (CRT). A meta-analysis of data from 37 randomised trials including over 9000 patients was conducted. For early-stage patients, CRT resulted in longer survival and longer HD-free survival than either RT or CT alone. Second malignancy (SM) risk was lower with CRT than with RT (no difference in between CRT and CT was demonstrated). For advanced stages, no difference in survival between CRT and CT was established. With CRT, HD-free survival was longer but SM risk was higher.

BACKGROUND

Description of the condition

Hodgkin's disease (HD), also known as Hodgkin's lymphoma, is a malignancy of the lymph nodes and lymphatic system with possible involvement of other organs (Mauch 1999; De Vita 2000). HD is closely related to the non-Hodgkin lymphomas. The disease is rare, with an annual incidence of approximately 3/100 000 in most countries, although in certain low-income countries the incidence in children is higher and EBV association and mixed cellularity subtype are more frequent (Mueller 1999). Most sufferers are young people, the incidence being greatest in the 3rd decade of life (Mueller 1999). The malignant cells stem from lymphocytes, but the causes of the malignancy are poorly understood (De Vita 2000). Untreated, HD is fatal within a few years in most cases, but today the large majority of patients are cured.

Description of the intervention

Treatment strategies are determined by disease stage and other prognostic factors. Early stage patients without adverse factors receive either radiotherapy (RT) alone, chemotherapy (CT) alone or a combination of mild CT with limited RT (CRT). Early stage patients with adverse prognostic factors are usually treated with moderate CT combined with RT. Advanced stage patients receive intensive CT, typically 6-8 cycles, with or without RT (De Vita 2000, Connors 2001, Diehl 2003, Kogel 2003, Meyer 2004).

The carcinogenic effects of ionising radiation were demonstrated in the 1930s, and since then its potential for causing almost any kind of cancer has been demonstrated (Boice 1988). Risks appear to be higher for young people. At low doses the risk increases linearly with dose; at therapeutic doses a further increase with dose was seen in certain sites but not in others. In contrast, the carcinogenicity of chemotherapy was only discovered in the 1960s with the development of effective combination regimens. Several alkylating agents and, more recently, topoisomerase II inhibitors, are recognised as causing leukaemia, whereas the role of other drugs and the possible link with other cancers (with the exception of that between cyclophosphamide and bladder cancer) are unknown. Due to the high rate of cure of HD patients and their predominantly young age, they have ample 'opportunity' to develop treatment-related second malignancies.

How the intervention might work

The optimal treatment modality (RT alone, CT alone or CRT), is still controversial. Relevant criteria include

- (a) efficacy in controlling HD,
- (b) options and prognosis for second-line therapy for those for whom first-line treatment fails and
- (c) acute toxicity, late effects and quality of life.

As cure rates of HD patients have dramatically improved over recent decades, so that today the great majority of even advanced stage patients reach a lasting complete remission, treatment toxicity and subsequent quality of life have increased in importance. Secondary malignancies (SM) are perhaps the most serious late effect of treatment (Henry-Amar 1996). SM can be divided into three classes: acute leukemias (AL), non-Hodgkin lymphomas (NHL) and solid tumours (ST). Secondary AL occur typically 3 to 5 years after chemotherapy treatment, reaching a cumulative risk of 1 to 3 per

cent in most studies. Secondary NHL occurs at a constant rate of about 0.2 per cent per year independent of treatment type. Secondary ST usually occur later, typically 5 to 20 years after treatment, with no evidence of a decline in incidence even after 20 years; cumulative incidences of up to 34 per cent have been estimated, representing a relative risk of up to five compared with the general population. ST appear to occur after both radiotherapy and chemotherapy. The impact of SM on the long-term survival of HD patients is considerable: the five-year overall survival rates after diagnosis of a second malignancy after HD were estimated as less than 10% for AL and about 30% for NHL and ST (Henry-Amar 1992).

Why it is important to do this review

The effect of treatment modality on SM rates has been investigated in several analyses of large data sets, including many that were pooled over several patient cohorts (Tucker 1988; Pedersen-Bjerg 1987; Henry-Amar 1992; Swerdlow 1992; Abrahamsen 1993; Hancock 1993; Rodriguez 1993; Biti 1994; Dietrich 1994; van Leeuwen 1994a; Bhatia 1996; Mauch 1996b; Aisenberg 1997; Birdwell 1997; Enrici 1998; Metayer 2000; Swerdlow 2000; van Leeuwen 2000; Dores 2002; Ng 2002, Josting 2003). Case-control studies have also been performed (Kaldor 1990, Kaldor 1992; van Leeuwen 1994b; Boivin 1995; van Leeuwen 1995; Brusamolino 1998; Swerdlow 2001). These citations include all identified studies which analysed at least 50 SM or at least 20 SM of a particular type (i.e., AL, NHL or a certain ST site). Other authors, such as Aleman 2003, investigated long-term cause-specific mortality after HD, including the relationship between SM and treatment modality. The relationship between treatment and SM risk has been reviewed by e.g. Henry-Amar 1993, Tucker 1993 and Ng 2004. Whilst it is widely accepted that AL is largely chemotherapy-induced and NHL is largely independent of treatment modality, it is unclear which, if any, treatment modality can help to avoid ST (see Table 1, Table 2, Table 3). The conclusions of the various investigators who compared ST risks after RT, CT and CRT are far from unanimous. The situation is complicated by the large number of anatomic sites at which a ST can occur, as well as by the much higher risk of ST in the general population (compared with the very low risk of AL and NHL). Further, this risk varies widely according to age, sex and other personal and environmental factors. The quality and quantity of relevant data on ST incidence is limited because of their very late occurrence.

The above-mentioned studies make non-randomised comparisons of SM rates between treatments, since even if randomised trial data were included, the data from several trials and also from non-randomised cases were pooled. Therefore, the benefits of randomisation do not necessarily apply to the treatment comparisons made in these studies: the patients receiving different treatment modalities may be non-comparable with respect to several known or unknown factors, which may be related to SM risk. In short, these comparisons may be 'confounded'.

However, the existence of these reports indicates that long-term data on SM incidence for patients in randomised trials have been collected by several institutions and study groups.

One literature-based and two individual-patient-data meta-analyses comparing different treatment modalities in HD have already been published (Shore 1990; Specht 1998; Loeffler 1998). The results demonstrate that the use of combined modality therapy improves disease-free survival, compared with CT alone (advanced

stages) or RT alone (early stages), but the 10-year overall survival rates were not significantly improved. Additional RT was in fact associated with a slightly lower overall survival compared with the use of further CT in advanced disease. Similarly, more extensive RT improved disease-free survival but not overall survival compared with limited RT. No meta-analysis included data on occurrence of second malignancies. However, [Loeffler 1998](#) analysed leukaemia-related deaths; survival estimates were limited to 10 years after HD diagnosis, too early for the effect of solid tumours to be felt. [Specht 1998](#) analysed SM-related deaths for patients without recurrence of HD.

In order to clarify the relationship between treatment modality and SM risk, long-term follow-up data from large numbers of patients are required, since only a small percentage will incur a SM within a given time interval. Further, specific sites of ST may have to be analysed separately, resulting in even smaller incidences. Due to the many confounding factors (age, sex, smoking habits, etc.), it is essential that conclusions are based on randomised comparisons between treatment modalities, in contrast to the many pooled data analyses already published. Finally, the varying SM incidences in the general population in different countries mean that an international overview is needed, since relative risks estimates or the recommendations based on data from one country may not apply elsewhere. All these factors argue for a systematic overview of the risk of SM.

A review of this type compares treatment 'policies', i.e. the choice of first-line treatment modality, rather than the influence of radiation and drugs on a biologic level. Not only these two influences but also accompanying diagnostic procedures, supporting medication, second-line treatment if necessary and treatment for other late effects may contribute to the overall SM risk associated with a treatment policy. Conclusions concerning the biologic influence of radiation and drugs per se must remain tentative.

Although an assessment of SM risks relative to the general population would be interesting, this is not attempted in the present review. Strictly, such an assessment is not possible on the basis of data from clinical trials, since the patients included are a non-random selection from the population of people with HD. They may differ from the HD population and from the general population with respect to various factors associated with SM risk, besides the factor assigned treatment. The relevant information for selection of treatment is the SM risk for one treatment relative to another (or the corresponding excess risk), and not the risk relative to the general population. The latter is best assessed using population-based comparisons with cancer registry data.

Due to the influence of personal factors on SM risk, to the many types of SM and to the time-to-event nature of the data, a meta-analysis based on individual patient data (IPD) makes best possible use of the information available. We collected data on all three classes of SM as well as on efficacy (overall and progression-free survival). We compared the effect of treatment modality on risk of SM as a whole as well as AL, NHL and ST, overall and disease-free survival. The efficacy comparison updates and extends the two previous IPD meta-analyses mentioned above. Furthermore, information on efficacy is needed to put the results concerning SM risk into context, since all outcomes must be considered together in choosing the optimal treatment modality. Since efficacy of treatment may be sensitive to particulars such as extent of disease, drug combination and dose, further evidence from the many

randomised trials comparing the efficacy of particular protocols must also be considered but is outside the scope of the present review.

OBJECTIVES

The main objective was to assess and compare the risks of secondary ST, secondary NHL and secondary AL in Hodgkin's disease patients following treatment with RT alone, CT alone and combined CRT. Risks due to involved and extended field radiotherapy were also compared. Risks due to the first-line therapy alone and additional risks due to salvage treatment for progressing and relapsing patients were investigated. Except as a means of assessing data quality, no attempt was made to estimate SM risks relative to the general population.

Further, the overall and progression-free survival rates following these interventions were compared. The results concerning SM were assessed in the light of this information. Conclusions were drawn concerning the advantages and disadvantages of each treatment modality for relevant categories of patients.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing different treatment modalities (see "types of interventions") which enrolled at least 30 patients and which finished recruitment before or during 2000. Smaller studies were considered to contribute negligible evidence, especially concerning SM, and to be prone to early termination bias or publication bias.

Types of participants

Adult or paediatric patients treated for newly diagnosed Hodgkin's disease.

Types of interventions

- Comparison of two or more of the following modalities:
 - Radiotherapy alone (RT)
 - Chemotherapy alone (CT)
 - Combined chemo- and radiotherapy (CRT)

'Chemotherapy' was restricted to multi-drug regimens similar to or succeeding those pioneered by De Vita and coworkers ([De Vita 1967](#)).

- Trials comparing involved field (IF-) RT versus more extensive (EF-) RT, either alone or combined with chemotherapy in each arm.

Ideally the treatment arms should differ only with respect to one modality. For instance, in comparing RT with CRT, the radiotherapy should be identical in each arm. However, in order to maximise the number of patients included, data from 'confounded' trials, allowing minor differences in the modality common to both arms, were also included.

Types of outcome measures

Primary outcomes

Primary endpoint was the time to occurrence of a secondary malignancy or last information (SM).

Secondary outcomes

Secondary endpoints were time to death of any cause (overall survival, OS) and time to Hodgkin treatment failure (progression, relapse or death of any cause: progression-free survival, PFS). The primary endpoint was analysed separately for each of the three classes of secondary malignancy (ST, NHL and AL), censoring at occurrence of the other two classes respectively. ST were analysed separately for the most frequent sites. Analyses were repeated with and without censoring at Hodgkin treatment failure, in order respectively to exclude or include the effects of second-line therapy.

Search methods for identification of studies

Electronic searches

Electronic literature databases:

- Cochrane Controlled Trials Register
- PubMed
- EMBASE
- CancerLit
- LILACS

Only reports published in 1975 or later were retrieved.

PubMed was searched using the algorithm of [Robinson 2002](#) to find RCTs.

Electronic searches

Electronic literature databases:

- Cochrane Controlled Trials Register
- PubMed
- EMBASE
- CancerLit
- LILACS

Only reports published in 1975 or later were retrieved.

PubMed was searched using the algorithm of [Robinson 2002](#) to find RCTs.

Searching other resources

- Conference proceedings: American Society of Clinical Oncology, American Society of Hematology, International Symposium on Hodgkin's Disease (Cologne), International Conference on Malignant Lymphoma (Lugano), American Society for Therapeutic Radiology and Oncology, European Society for Medical Oncology, European Society for Therapeutic Radiology and Oncology - all 1980 to 2001
- Lists of clinical trials maintained by the United States National Cancer Institute and the United Kingdom Coordinating Committee on Cancer Research
- Reference lists of all relevant retrieved publications

- Contact with cooperative trial groups working on Hodgkin's disease, identified through personal contacts and conference proceedings
- Previous meta-analyses in HD.

Data collection and analysis

Individual patient data were requested from each trial identified as meeting the inclusion criteria, including data on date of birth, sex, date of (first) Hodgkin diagnosis, stage of disease, presence/absence of systemic (B) symptoms, treatment arm by randomisation, date of randomisation, remission status at end of first-line treatment (with date), occurrence and date of relapse, occurrence, date and type of SM, whether SM occurred in the radiation field (if applicable), occurrence and date of death and date of last follow-up information. IPD were checked for completeness and consistency. All patients randomised into the trial were included (intent-to-treat), unless the first diagnosis of HD was reported as erroneous. As a preparatory step, each trial was analysed separately, comparing the treatment arms with respect to recruitment times, patient characteristics, complete remission rate, length of follow-up, PFS, OS and occurrence of SM. This step investigates the comparability of the treatment arms and the consistency of the data with previous publications of the trial. Each trial was assessed for the following aspects of trial quality:

- Randomisation method. Any aspects of randomisation method or characteristics of the data set (see above) which could imply inadequate concealment or systematic differences in recruitment into the respective treatment arms were noted and queried.
- Adherence to intent-to-treat in the data set. The possibility of post-randomisation exclusions from or swaps between the treatment arms was assessed.
- Reliability of SM follow-up methods. The method of follow-up as described by the trialists was assessed for likely completeness and accuracy.
- Completeness of follow-up. The median follow-up time, using the Kaplan-Meier method, was calculated to indicate average length of follow-up. The distribution of last information dates was quantified. Both high variability (large interquartile range), in relation to the median follow-up time, and significant differences between treatment arms indicate less reliable follow-up. Completeness of follow-up was also compared between patients with and without SM.
- SM rate was compared with that expected in an age and sex matched cohort from the general population, using data from various US and European cancer registries.

The last two aspects are seen to be the most problematic, since SM events were not a major endpoint for most trials, and some trials recruited decades prior to this review.

The following randomised comparisons were combined across the appropriate trials:

- RT versus CRT
- CT versus CRT
- RT versus CT
- IF-RT versus EF-RT.

Firstly, a measure of the difference in SM incidence (or other endpoint, respectively) between the treatment arms of each trial separately was calculated, together with an estimate of the variance of this quantity (Method of Peto: [EBCTCG 1988](#), [EBCTCG 1992](#)). These measures were combined across trials relevant to the comparison being made, in order to assess overall differences in SM rate between modalities. This step provides a model-free assessment of the relative risks for SM of different modalities, i.e. of the treatment effect.

Relative risks refer to randomised comparison between treatment modalities. Risks relative to the general population were calculated only for the purpose of assessing data quality.

As sensitivity analysis for SM, the data for all trials making a particular comparison of modalities were analysed together by Cox proportional hazards regression ([Cox 1972](#)) including relevant covariates (age, sex, stage). In order to preserve the advantages of randomised comparisons in the presence of inter-trial heterogeneity of baseline risk, analyses were stratified by trial.

Heterogeneity of treatment effects between trials was tested for. In addition, subgroup analyses were performed to investigate whether certain types of patient, disease stage or treatment type show different treatment effects. The following patient-related subgroups were employed: stage (early stage = I and II, advanced stage = III and IV), age (0-15 years, 16-39 years, 40-59 years, 60 years and older) and sex. Treatment-related subgroups were: extent of RT (IF, more than IF) for CT vs. CRT, type of CT (anthracyclin-containing, others) for RT vs. CRT and CT vs. CRT.

Both the first-line treatment and possible salvage therapy for progression or relapse of HD may contribute to SM risk. The type and frequency of salvage therapy, and thus its effect on SM risk, depend on both the nature and efficacy of the first-line treatment. Therefore, separate analyses were conducted with and without the effect of salvage therapy. For the latter, follow-up times were censored at HD progression/relapse and subsequent SM did not count as events.

ST were analysed separately for the most common sites (lung and breast).

Further sensitivity analyses were performed to check that the results are not crucially dependent on selection criteria or analysis methods. Firstly, analyses were repeated with the exclusion of the latest, less complete follow-up periods in each trial (i.e. when less than 75% of patients were still in follow-up). Secondly, analyses were rerun excluding confounded trials. Thirdly, SM and ST analyses were repeated excluding non-melanoma skin cancers (as in many previous investigations of SM). Fourthly, the cumulative incidence method ([Pepe 1993](#), [Tai 2001](#)) which allows for competing risks (deaths from other causes compete with second malignancies) was adapted to permit a trial-stratified analysis according to Peto's method, and the results qualitatively compared with the main analysis.

Due to the multiplicity of endpoints and to the several subgroup analyses proposed, the danger of significant differences arising by chance alone is increased. For this reason, 99% confidence intervals were employed for individual trials, but 95% intervals are shown for aggregated estimates (as in e.g. [EBCTCG 1992](#)).

RESULTS

Description of studies

The search, including the appraisal of abstracts and of full articles where necessary, identified a total of 76 eligible trials. One of these trials was rejected after correspondence with the authors because it was not randomised. One further trial was rejected because no SM were recorded in the data received, and it seemed that this information had not been collected.

Although trials with less than 30 patients were to be excluded, we included a number of small Stanford University trials by amalgamating those with similar design and simultaneous or adjacent recruitment periods. In many cases, this involved amalgamation of studies which administered the same or very similar treatment to patients with slightly different stage of disease. The amalgamated cohorts were analysed as if they represented single trials. One data-set which was received as a single trial was split into two trials for the analysis, each containing less than 30 patients, since two distinct study designs were applied to two groups defined by stage ([SJCRH, HD study II B](#); [SJCRH, HD Study IIC](#)). In total, IPD from 37 trials could be analysed, including 4 trials which contributed to more than one treatment comparison. The appropriate treatment arms of these trials were analysed within each relevant comparison without making any adjustment for the multiple use of the same data.

IPD could not be obtained for a large number of otherwise eligible studies, which are listed in the table of excluded studies. The percentage of eligible IPD obtained and analysed is given below in separate descriptions of the studies for each treatment comparison. Amalgamated Stanford trials are counted as one study.

RT vs. CRT

(See section 03 in data and analyses)

15 studies with 3343 patients in total were included in the analysis. 12 trials were excluded because data could not be obtained. The included patients represent 68% of those in all eligible identified trials for this treatment comparison. The included trials recruited between 24 and 627 patients. The earliest trial recruited in 1966 to 71 and the latest in 1994 to 98. Most trials were for early stage patients (stages I to II) only (3054 patients), while 3 trials also enrolled stage III patients (289 patients).

8 trials had an unconfounded design, i.e. the same radiotherapy was planned in each treatment arm. Radiotherapy was extended field (EF) in most studies, involved field (IF) in only one study. 7 trials were confounded, with subtotal nodal irradiation (STNI) or total nodal irradiation (TNI) in the RT arm and IF or mantle-field in the CRT arm. Various chemotherapy regimens were employed, most commonly MOPP or ABVD, typically with 6 cycles. The 9 earlier trials used a regimen without any anthracycline whereas the 6 more recent trials used a regimen including doxorubicin or (in one) epirubicin.

CT vs. CRT

(See section 02 in data and analyses)

16 studies with 2861 patients in total were included in the analysis. 12 trials were excluded because data could not be obtained. The included patients represent 53% of those in all eligible identified trials for this treatment comparison. The included trials recruited

between 24 and 473 patients. The earliest trial recruited in 1966-71 and the latest in 1990-2000. There were 696 early stage (I-II) and 2165 advanced stage (III-IV) patients.

10 trials had a purely unconfounded design, i.e. identical chemotherapy was specified for each treatment arm, typically 6 cycles of a MOPP-like regimen or ABVD. Only the 4 most recent trials included an anthracyclin (doxorubicin). 3 trials were partially confounded, specifying 10-12 cycles in the CT arm in certain cases, whereas in the CRT arm 6 cycles of the same regimen were specified for all cases. Further, 3 trials were wholly confounded, with 8-12 cycles in the CT arm and 6 in the CRT arm for all patients. Radiotherapy in the CRT arm ranged from IF 6 (trials) to TNI (4 trials). The earliest 5 trials (1966-74) used EF or TNI whereas the majority of subsequent trials used IF.

RT vs. CT

(See section 01 in data and analyses)

3 studies with 415 patients (57% of those in eligible identified trials) in total were included, while 3 trials were excluded because data were not obtained. The included trials enrolled between 94 and 205 patients, and all recruited within the time period 1973-88. Two trials recruited stages I-II (299 patients) and one recruited stage III (116 patients). Mantle field, EF and TNI radiotherapy were compared with 6 cycles of MOPP, BOPP and ABVD, respectively.

IF-RT vs. EF-RT

(See section 04 in data and analyses)

10 studies with 3221 patients in total (2926 early stages, 295 advanced stages) were included in the analysis. 3 trials were excluded because data could not be obtained. The included patients represent 69% of those in all eligible identified trials for this treatment comparison. The included trials recruited between 45 and 1136 patients. The earliest trial recruited in 1966-71 and the latest in 1993-98. 8 trials were mainly for early stage patients and 2 mainly for advanced stages.

2 studies (only 259 patients in total) planned no chemotherapy, 6 planned identical chemotherapy in each arm and 2 specified, in certain cases, more cycles of the same regimen in the IF arm than in the EF arm (i.e., partially confounded). The chemotherapy regimens were MOPP-like, MOPP/ABVD-like or ABVD (except in one study, which administered mechlorethamine+vinblastine), usually with 3-6 cycles.

Risk of bias in included studies

Randomisation method

This information was requested in a questionnaire to trialists, supplemented using trial protocols and publications, and the IPD were checked for consistency with these. For 16 trials, no details were received but we found no other indication of inadequacy. 17 responses indicated reliable methods (central computer-based randomisation in 8 trials, sealed envelopes in 9 trials), providing adequate concealment. One trial ([Obninsk, R 18](#)) randomised using date of birth; however, the data did not agree with the method stated.

In one trial ([Obninsk, advanced](#)) randomisation rates during the various years of recruitment were not always balanced between treatment arms, suggesting that randomisation was not uniformly employed throughout recruitment. In another trial ([Lygra I](#)) considerable more patients were assigned to the EF-arm (31) than to the IF-arm (19). In 2 trials ([GATLA 9-H-77](#); [Stanf. C7-10, C12-15](#)),

significant imbalances in the distribution of patients' ages were noted between treatment arms.

Intention-to-treat

For one trial ([Lygra II](#)) it had been necessary to 'rescue' and reinstate patients assigned to each treatment arm who had apparently been deleted from the lists kept by the trialists at that time.

In 3 trials ([Rome, HD 94](#); [GATLA 9-H-77](#); [Rome/Florence](#)) there were discrepancies between the published recruitment period or number of patients and the IPD.

Various studies excluded patients from their own analyses because they were not treated 'per protocol' or were lost to follow-up. We reincluded such patients as far as allowed by the information available to us.

Follow-up methods for second malignancies

We asked for the relevant details in a questionnaire to trialists which was returned for 24 out of 37 trials. Most of these 24 studies collected information on SM only as part of routine follow-up documentation. Special questionnaires on SM were employed in 5 trials. Information from the relevant cancer registry was used in 5 studies. For 8 trials, SM data were claimed to be complete for all patients, whereas for 16 trials the SM data were described as 'probably incomplete'.

All SM were classifiable as AL, NHL or ST in 31 trials. This classification was possible for some cases only in 3 trials, one trial distinguished only between AL and other SM and in one trial ([CALGB 6604](#)), the two SM cases, although not classified, were evaluated as malignant melanoma as reported by [Hoogstraten 1979](#). In one trial ([CALGB 7751](#)) no SM were recorded.

Details of all solid tumour sites were supplied for 31 trials, for some cases only in 3 trials and not at all in 2 trials.

Completeness of follow-up

This aspect was assessed using the IPD themselves. Firstly, the median follow-up time (MFU) was calculated. Secondly, the interquartile range in the date of last information (IQR-DLI) was computed and compared with median follow-up. 12 trials had a MFU between 4 and 9 years, 13 trials between 10 and 19 years and 12 trials between 20 and 32 years. The IQR-DLI was less than 12 months in 11 trials, between 12 and 23 months in 6 trials, between 24 and 47 months in 10 trials and between 4 years and 13 years in 10 trials. The IQR-DLI was less than 10% of the MFU in 12 trials and between 10% and 20% in 8 trials. Comparing the various trials within study groups, the IQR-DLI tended to increase linearly with MFU up to a MFU of about 20 years; for trials with a MFU longer than 20 years the IQR-DLI was lower (between 0 and 5 years). This may indicate increasing loss to follow-up as trials get older, but that the oldest trials where data are still available have employed effective update campaigns or used registry data to improve completeness.

The distribution of lengths of follow-up was also compared between treatment arms within trials. In one trial only, a significant difference was detected. Bearing in mind the multiple comparisons involved, therefore, no evidence of preferential follow-up in particular treatment arms was found.

The completeness of SM reporting was studied by comparing the observed number of SM cases in each trial with the number expected in a cohort with the same age and gender structure based

on cancer registry results. For all trials together, the relative risk of SM (observed/expected) lay between 3.2 (using US SEER registry data) and 3.8 (using Netherlands registry data). Using SEER data, the observed number was less than the expected number for 3 trials (Mexico, 82HO31: 5 vs. 11.0, CALGB 6604: 2 vs. 2.2, CALGB 7751: 0 vs. 1.8). Relative risk was between 1.0 and 2.0 for 6 trials, between 2.0 and 6.0 for 22 trials and more than 6.0 for 6 trials.

Effects of interventions

RT vs. CRT

Peto estimated rates are shown in Table 4 (early stages) and Table 5 (advanced stages). Data and analyses see outcome 03.

Progression-free and overall survival

PFS was significantly better with CRT than with RT alone ($P < 0.00001$, Peto odds ratio (POR) = 0.49 for all stages together, see Figure 1). This result applies to both early and advanced stage patients, but the odds ratio for the early stages (0.46) was significantly more extreme (test for interaction: $P = 0.014$) than that for the advanced stages (mainly IIIA; 0.72). The PFS treatment effect increased during the first 5 years after HD diagnosis; afterwards, the difference in PFS rates remained constant at circa 15 to 20%.

Figure 1. Forest plot of comparison: 3 RT v CRT, outcome: 3.7 progression free survival.

OS was significantly better with CRT than with RT alone ($P = 0.0004$, POR = 0.76 for all stages together, see Figure 2). This result refers mainly to early stage patients; there were only 289 advanced stage

patients. The OS treatment effect appeared during the first 5 years after SPT and increased gradually to circa 9% at 30 years after HD diagnosis.

Figure 2. Forest plot of comparison: 3 RT v CRT, outcome: 3.1 overall survival.

Younger adults tended to have a larger PFS treatment effect in favour of CRT than older patients (trend test: $P = 0.037$). There were no other significant subgroup differences according to age or sex in OS or PFS ($P \geq 0.11$).

There was substantial heterogeneity in treatment effects between trials both in PFS (I-square 77%, $P < 0.00001$) and OS (I-square 56%, $P = 0.003$). PFS treatment effects tended to increase from the oldest (1966) to the most recent (1998) recruitment periods. The 6 most recent trials were exactly those which administered an anthracycline-containing chemotherapy. No clear time-trend was discernable for OS, although the significance of the treatment effect favouring CRT was due largely to two fairly large trials (Mexico, 82HO31 and EORTC-GELA, H8F) which included doxorubicin.

Results for OS and PFS remained largely unchanged when the 7 (of 15) confounded trials were excluded. Likewise, censoring at the 75% cut-off date for each trial did not change the results for PFS (not performed for OS).

Second malignancies

There was a consistent trend to higher overall risk of SM with RT alone compared with CRT ($P = 0.03$, POR = 0.79 for all stages together, Figure 3). This effect was most marked in advanced stage patients ($P = 0.02$, POR = 0.45) and did not reach significance in early stage patients ($P = 0.14$, POR = 0.84). In early stages, there was no arm difference until 10 to 15 years after HD diagnosis, and the difference increased steadily thereafter up to 11% until 30 years after HD diagnosis. In advanced stages the difference was already apparent at 5 years after HD diagnosis and widened steadily up to 19% until 25 to 30 years after HD diagnosis (Figure 4).

Figure 3. Forest plot of comparison: 3 RT v CRT, outcome: 3.14 second malignancy free survival.

Figure 4. RT v CRT SM Peto. Graphs of Peto estimated cumulative SM rates comparing RT with CRT. Left: all SM; right: censored at relapse or progression of HD. Below each graph the numbers of patients still 'at risk' are displayed.

The treatment effect of higher SM risk with RT alone was also seen when considering ST only ($P = 0.05$, $POR = 0.78$, [Figure 5](#)) and when considering NHL only ($P = 0.03$, $POR = 0.46$, early stages only, [Figure](#)

[6](#)). AL risk was higher (though not significantly so) with CRT ($P = 0.21$, $POR = 1.55$ for early stages, [Figure 7](#)). No treatment effects were seen when considering lung cancer alone or breast cancer alone.

Figure 5. Forest plot of comparison: 3 RT v CRT, outcome: 3.26 solid tumors.

Figure 6. Forest plot of comparison: 3 RT v CRT, outcome: 3.34 NHL - early stages only.

Figure 7. Forest plot of comparison: 3 RT v CRT, outcome: 3.32 AML/MDS - early stages only.

When follow-up was censored at progression or relapse of HD, the SM treatment effect largely disappeared in both early and advanced stages (P = 0.51, POR = 1.11 for all stages together, Figure 8; Figure 9). Similar results were seen when considering ST only (Figure 10) or NHL only (Figure 11), although lung cancer risk (censoring at

progression/relapse) was somewhat higher with CRT (P = 0.11, POR = 1.84). However, for AL only there was a significantly higher risk with CRT (P = 0.01, POR = 3.40, Figure 12) when censoring at progression/relapse.

Figure 8. Forest plot of comparison: 3 RT v CRT, outcome: 3.18 SM before progression/relapse.

Figure 9. RT v CRT SM CRisks. Graphs of competing risks cumulative SM incidences comparing RT with CRT. Left: all SM; right: censored at relapse or progression of HD. Below each graph the numbers of patients still 'at risk' are displayed.

Figure 10. Forest plot of comparison: 3 RT v CRT, outcome: 3.28 solid tumors before progression/relapse.

Figure 11. Forest plot of comparison: 3 RT v CRT, outcome: 3.35 NHL before progression/relapse.

Figure 12. Forest plot of comparison: 3 RT v CRT, outcome: 3.33 AML/MDS before progression/relapse.

There were no significant subgroup differences in SM treatment effect according to age or sex. Neither was a time-trend according to recruitment years discernable, nor a difference in SM treatment effect between trials administering anthracycline and the others, nor between those administering mustargen and the others. Heterogeneity in SM treatment effect between trials was non-significant ($P = 0.14$) and moderate (I-square 29%).

The SM treatment effect remained of similar size but became non-significant when the 7 confounded trials were excluded ($P = 0.21$, $POR = 0.82$). Likewise, censoring at the trial-specific 75% cut-off date gave concordant but non-significant results ($P = 0.24$, $POR = 0.86$). The exclusion of non-melanoma skin cancers also led to concordant results of reduced significance ($P = 0.09$, $POR = 0.81$). The use of the Cox regression method gave similar results to the Peto method ($P = 0.05$, Hazard ratio = 0.80). Peto-based competing risks analysis of overall SM risk calculated lower risks in both arms compared to the standard Peto method, but the treatment effect (i.e., difference between the treatment arms) remained similar. Competing risks analysis censored at progression/relapse (counting progression, relapse and death as competing events) calculated higher SM risks with CRT (this is to be expected since in this analysis the higher relapse rate with RT alone reduces the chance of the patient being 'at risk' of SM in later years) (Figure 9).

CT vs. CRT

Peto estimated rates are shown in Table 6 (early stages) and Table 7 (advanced stages). Data and analyses see outcome 02.

Progression-free and overall survival

PFS was significantly better with CRT than with CT alone ($P < 0.0001$, $POR = 0.77$ for all stages together, Figure 13). This result applies to both early and advanced stage patients, but the odds ratio for the early stages (0.60) was significantly more extreme (test for interaction: $P = 0.032$) than that for the advanced stages (0.83). The PFS treatment difference became apparent within the first year after HD diagnosis and increased to about 7% after 3 years (advanced stages) or 17% after 10 years (early stages), respectively, these differences remaining constant thereafter until 25 years.

OS did not differ significantly between CT and CRT ($P = 0.12$, $POR = 0.90$ for all stages together, tending to favour CRT, Figure 14). For early stages alone, OS was significantly better with CRT ($P = 0.006$, $POR = 0.62$). However, the 4 trials involving early stages showed very heterogeneous results: no difference for the two older trials, but odds ratios of 0.38 and 0.28 for the two more recent trials. The OS curves were almost identical for the advanced stages, while for the early stages they resembled those for PFS, the 12% difference after 10 years shrinking in this case towards 9% after 20 years.

Figure 13. Forest plot of comparison: 2 CT v CRT, outcome: 2.10 progression free survival.

Figure 14. Forest plot of comparison: 2 CT v CRT, outcome: 2.1 overall survival.

For advanced stages, there was a significant trend towards PFS being better with CRT for younger patients (children; adults under 40) and slightly better with CT for older patients (60 and older), with no treatment effect for the 40 to 59-year-olds (trend test: $P = 0.0051$). A similar trend was seen in OS, but this was not significant ($P = 0.19$). For early stages, no significant age-related differences in OS or PFS effects were seen ($P \geq 0.074$). No significant differences in OS or PFS treatment effect between males and females were seen ($P \geq 0.27$).

There was substantial heterogeneity in treatment effects between trials both in PFS (I-square 51%, $P = 0.009$) and OS (I-square 58%, $P = 0.002$). PFS treatment effects in advanced stages tended to decrease in size from the earliest (1966) to the most recent (1989) recruitment periods. Thus, the largest benefits of CRT in PFS were associated with non-anthracyclin-containing chemotherapy and/

or more extensive radiotherapy. There was no clear analogous tendency in OS.

OS and PFS results remained largely unchanged when the 6 (wholly or partially) confounded trials were excluded (OS: $P = 0.06$, $POR = 0.83$; PFS: $P < 0.0001$, $POR = 0.68$). PFS results were not relevantly affected by censoring at the 75% cut-off date (not performed for OS).

Second malignancies

SM risk was higher with CRT than with CT alone ($P = 0.05$, $POR = 1.38$ for all stages together. Figure 15), but the difference was not significant in early stage patients alone ($P = 0.73$, $POR = 1.17$). The difference in cumulative risk for advanced stages became apparent 5 years after HD diagnosis and increased to a maximum of 4% from 10 to 15 years after HD diagnosis; thereafter the difference disappeared (Figure 16).

Figure 15. Forest plot of comparison: 2 CT v CRT, outcome: 2.17 second malignancy free survival.

Figure 16. CT v CRT SM Peto. Graphs of Peto estimated cumulative SM rates comparing CT with CRT. Left: all SM; right: censored at relapse or progression of HD. Below each graph the numbers of patients still 'at risk' are displayed.

The treatment effect was seen in AL alone: for all stages together, $P = 0.07$, $POR = 1.82$ (Figure 17). There was no treatment effect for NHL (Figure 18), and the effect for ST alone was not significant ($P = 0.26$, Figure 19).

The effects were largely unchanged, but favoured CT somewhat more strongly, if follow-up was censored at progression and

relapse: $P = 0.01$, $POR = 1.60$ for all stages together (Figure 20), no difference for early stages alone ($P = 0.96$). In this case, there were somewhat more ST ($P = 0.07$, $POR = 1.60$, Figure 21) and significantly more AL ($P = 0.01$, $POR = 2.75$, Figure 22) with CRT than with CT (but no difference in NHL, Figure 23).

Figure 17. Forest plot of comparison: 2 CT v CRT, outcome: 2.33 AML/MDS.

Figure 18. Forest plot of comparison: 2 CT v CRT, outcome: 2.35 NHL.

Figure 19. Forest plot of comparison: 2 CT v CRT, outcome: 2.28 solid tumors.

Figure 20. Forest plot of comparison: 2 CT v CRT, outcome: 2.21 SM before progression or relapse.

Figure 21. Forest plot of comparison: 2 CT v CRT, outcome: 2.30 solid tumors before progression/relapse.

Figure 22. Forest plot of comparison: 2 CT v CRT, outcome: 2.34 AML/MDS before progression/relapse.

Figure 23. Forest plot of comparison: 2 CT v CRT, outcome: 2.36 NHL before progression/relapse.

There were no significant subgroup differences in SM treatment effect according to age or sex. Inspection of the forest plot did not reveal any time-trend according to recruitment years nor a difference in SM treatment effect between trials administering anthracyclin and the others nor a difference between trials employing IF-RT versus those using EF-RT. There was no heterogeneity in SM treatment effect between trials (I-square 0%).

The SM treatment effect became smaller and non-significant if the 6/16 (wholly or partially) confounded trials were excluded ($P =$

0.28, $POR = 1.27$). In an analysis with censoring at the 75% cut-off date, the tendency to more SM with CRT became stronger ($P = 0.007$, $POR = 1.71$). The exclusion of non-melanoma skin cancers from the analysis led to concordant results of slightly reduced significance ($P = 0.09$, $POR = 1.32$ for all SM, all stages). Using Cox regression techniques, similar results with a somewhat stronger treatment effect ($P = 0.02$, hazard ratio = 1.45) were obtained. The competing risks analyses did not lead to any relevant changes in the treatment effect compared with the standard Peto analysis (Figure 24).

Figure 24. CT v CRT SM CRisks. Graphs of competing risks cumulative SM incidences comparing CT with CRT. Left: all SM; right: censored at relapse or progression of HD. Below each graph the numbers of patients still 'at risk' are displayed.

RT vs. CT

Peto estimated rates are shown in Table 8 (early stages) and Table 9 (advanced stages). Data and analyses see outcome 01.

Progression-free and overall survival

Neither PFS nor OS differed according to assigned treatment (PFS: $P = 0.93$, $POR = 0.99$ Figure 25; OS: $P = 0.34$, $POR = 1.17$, Figure 26).

Figure 25. Forest plot of comparison: 1 RT vs. CT, outcome: 1.4 progression free survival.

Figure 26. Forest plot of comparison: 1 RT vs. CT, outcome: 1.1 overall survival.

There were no relevant differences between male and female patients, with one exception: results favoured CT for females but RT for males in the early stages only (interaction test: $P = 0.23$ for OS and $P = 0.028$ for PFS). There were no such differences for advanced stages ($P \geq 0.26$). Age subgroups were not formed due to the small numbers of patients. Heterogeneity of treatment effect between the 3 trials was moderate for OS (I-square 41%, $P = 0.18$) and absent for PFS (I-square 0%).

Second malignancies

There was a non-significant increase in SM with CT compared to RT ($P = 0.13$, $POR = 2.12$ for all stages, Figure 27), which was more pronounced for early stage patients ($P = 0.05$, $POR = 3.37$) (Figure 28). There were insufficient events to analyse each type of SM (ST: 5 (RT) vs. 3 (CT); AL: 0 vs. 2; NHL: 1 vs. 3). In the analysis censoring follow-up at progression and relapse, no significant treatment effect was seen ($P = 0.30$, $POR = 1.99$, Figure 29).

Figure 27. Forest plot of comparison: 1 RT vs. CT, outcome: 1.8 second malignancy free survival.

Figure 28. RT v CT SM Peto. Graphs of Peto estimated cumulative SM rates comparing RT with CT. Left: all SM; right: censored at relapse or progression of HD. Below each graph the numbers of patients still 'at risk' are displayed.

Figure 29. Forest plot of comparison: 1 RT vs. CT, outcome: 1.9 SM before progression/relapse.

No significant differences in SM treatment effect between males and females were obtained ($P \geq 0.41$). Sensitivity analysis did not diverge from the main analysis. Censoring at the 75% cut-off date was not performed since the remaining number of events (0 vs. 7 SM known to have occurred before cut-off) was too small. The Cox regression method estimated a slightly stronger treatment effect ($P = 0.07$, hazard ratio = 2.55).

IF-RT vs. EF-RT

Peto estimated rates are shown in Table 10 (early stages) and Table 11 (advanced stages). Data and analyses see outcome 04.

Progression-free and overall survival

PFS was significantly better with extended field (EF) than with involved field (IF) radiotherapy ($P = 0.02$, $POR = 0.82$ for all stages together, Figure 30). This effect was in the same direction but not significant for the early stages only ($P = 0.26$, $POR = 0.90$, Figure 31). For advanced stages, a 22% difference in PFS developed during the first year after HD diagnosis and remained almost constant over 20 years.

Figure 30. Forest plot of comparison: 4 IF-RT vs. EF-RT, outcome: 4.8 progression free survival.

Figure 31. Forest plot of comparison: 4 IF-RT vs. EF-RT, outcome: 4.1 overall survival.

OS showed no treatment effect for all stages together (P = 0.29, POR = 0.91) but for the advanced stages was significantly better with EF-RT than with IF-RT (P = 0.01, POR = 0.66), the difference developed gradually over the first 5 years after HD diagnosis up to about 18%, then remained constant for about 20 years.

There was moderate heterogeneity in treatment effects between trials in PFS (I-square 29%, P = 0.17) and very little heterogeneity for OS (I-square 9%, P = 0.36). For both PFS and OS, the difference in treatment effect between early and advanced stages was significant (interaction tests: PFS: P = 0.047; OS: P = 0.024). No clear heterogeneity was apparent between studies with and without chemotherapy; however, the number of patients in the radiotherapy-alone studies was too small to allow a precise comparison. No difference in treatment effect between males and females was seen (P >= 0.070). For the early stages, both PFS and OS tended to be more favourable with IF-RT in patients 60 or more years old (treatment effect in this age group: PFS: P = 0.05, OS: P = 0.05; test for age trend: PFS: P = 0.027, OS: P = 0.063); there were too few advanced stage patients to expect to see a comparable effect (P >= 0.28).

Restricting the analyses to trials administering RT additional to CT, PFS and OS results were similar to the main analysis, except that no PFS treatment effect was seen in the early stages (P = 0.85, POR = 0.98).

Censoring at the 75% cut-off date did not change the PFS results at all.

Second malignancies

No significant difference in the SM rate between EF-RT and IF-RT was seen (P = 0.28, POR = 1.17 for all stages, tendency to more SM with EF-RT, Figure 32; Figure 33). No significant differences were seen in AL (Figure 34), NHL (Figure 35) or ST rates; for ST the treatment effect resembled that for all SM (P = 0.35, POR = 1.18 for all stages, Figure 36). For breast cancers alone there was a significantly greater risk with EF-RT (P = 0.04, POR = 3.25 in early stages; no breast cancers in advanced stages). For lung cancers there was a tendency (not significant) in the same direction (P = 0.22, POR = 1.73).

Figure 32. Forest plot of comparison: 4 IF-RT vs. EF-RT, outcome: 4.16 second malignancy free survival.

Figure 33. IF v EF SM Peto. Graphs of Peto estimated cumulative SM rates comparing IF-RT with EF-RT. Left: all SM; right: censored at relapse or progression of HD. Below each graph the numbers of patients still 'at risk' are displayed.

Figure 34. Forest plot of comparison: 4 IF-RT vs. EF-RT, outcome: 4.32 AML/MDS.

Figure 35. Forest plot of comparison: 4 IF-RT vs. EF-RT, outcome: 4.33 NHL.

Figure 36. Forest plot of comparison: 4 IF-RT vs. EF-RT, outcome: 4.27 solid tumors.

When follow-up was censored at progression and relapse, the tendency to more SM with EF-RT was slightly more pronounced but still not significant ($P = 0.09$, $POR = 1.54$, [Figure 37](#)).

Figure 37. Forest plot of comparison: 4 IF-RT vs. EF-RT, outcome: 4.20 SM before progression or relapse.

No significant differences in SM treatment effect were obtained according to stage, sex or age of patients ($P \geq 0.13$).

Censoring at the 75% cut-off date, exclusion of non-melanoma skin cancers, competing risks techniques (Figure 38) and Cox regression analysis each led to results closely consistent with the main analysis.

Figure 38. IF v EF SM CRisks. Graphs of competing risks cumulative SM incidences comparing IF-RT with EF-RT. Left: all SM; right: censored at relapse or progression of HD. Below each graph the numbers of patients still 'at risk' are displayed.

DISCUSSION

With the inclusion of 9312 patients, this systematic review is one of the largest investigations of second malignancies yet performed (the cohort study by [Dores 2002](#) and two embedded case-control studies, [Boivin 1988](#) and [Kaldor 1992](#) drew patients from larger collections). To the authors' knowledge, it is the only large study of SM employing randomised comparisons, with the exception of the previous meta-analysis by [Loeffler 1998](#) where leukaemia-related death was analysed in 1183 patients from 12 RCTs comparing CT with CRT. Randomised comparisons have otherwise been done only within single RCTs and thus with small numbers of events. The present comparison RT vs. CT is based on only 415 patients and 18 events and thus provides little reliable evidence. In contrast, the comparison RT vs. CRT included 3433 mainly early stage patients and 325 events, CT vs. CRT 2861 mainly advanced stage patients

and 164 events, and IF-RT vs. EF-RT 3221 mainly early stage patients and 201 events.

Concerning progression-free and overall survival, the present review is more comprehensive and included more patients (for the respective comparisons) than the previous published meta-analyses. The meta-analysis by [Shore 1990](#) based on published data compared RT vs. CRT in 2239 and EF-RT vs. IF-RT in 2110 early stage patients. [Specht 1998](#) compared, for early stages, IF-RT vs. EF-RT (1974 patients in 9 trials) and RT vs. CRT (1688 patients in 13 trials). [Loeffler 1998](#) compared CT vs. CRT in 1740 mainly advanced stage patients. However, these earlier meta-analyses each included a number of trials for which data could not be obtained for the present review. Furthermore, in the investigation by [Loeffler et al.](#) subgroups according to mediastinal involvement and bulky disease could be analysed separately (although no significant interactions between these variables and the treatment effect were detected).

Limitations of included studies

The large majority of studies used adequate methods of randomisation resulting in treatment cohorts well balanced with respect to basic patient characteristics. In many studies, certain randomised patients were excluded from the trialists' own analyses, whilst such exclusions did not conform to our intent-to-treat principle. In many cases we could not reinstate all such patients in our analysis: either the patients were not included at all in the data set, or information on outcome was missing.

Few trials managed to follow all surviving patients up to a uniform date of last information. Loss to follow-up resulted in a dispersion of dates of last information (largest interquartile range was nearly 10 years). This is a potential source of bias in estimating event rates. However, we found no evidence of a different follow-up pattern among the treatment arms of any trial, so that a bias in treatment effect is not suggested.

The greatest source of uncertainty, in the authors' opinion, is the reliability of reporting of second malignancies. On the one hand, SM events may be underreported in some trials. Particularly the earlier trials were not designed to provide information on SM risk, which was unknown at that time. The majority of trialists assessed their SM information as 'probably incomplete'. Few trialists had cross-checked with death or cancer registries. Comparison of SM rates observed in the included trials with those expected on the basis of cancer registry data implied serious underreporting in a few trials. On the other hand, SM rates may be overreported in the sense that patients without an event are more likely to be lost to follow-up. This unfortunately cannot be ascertained using the data themselves, since a fairly long follow-up is a prerequisite for observation of a SM, so follow-up times are systematically longer, on average, amongst patients having a SM, independently of any bias. These two possible errors lead to underestimation and overestimation of SM risk, respectively. Again, a bias in the estimation of treatment effect would result only if such SM reporting biases differed between treatment arms.

Methods of review

A large number of relevant trials could not be included in the meta-analysis because IPD could not be obtained. This might be a source of bias.

In order to obtain adequate numbers of SM events for reliable comparisons, trials spanning 4 decades and employing very varying diagnostic and therapeutic methods have been included. Treatment differences may vary widely according to the methods used, particularly chemotherapy regimen and radiotherapy technique. Irradiation techniques have advanced considerably since the 1960s (Tucker 1993) and this may have reduced SM risk. The use of new chemotherapy drugs, avoiding alkylating agents and preferring anthracyclin-containing combinations, has been shown to reduce the risk of second AL (Henry-Amar 1993). Subgroup analyses generally lack power to elucidate these variations reliably. Substantial heterogeneity in treatment effects was seen in OS and PFS for certain treatment comparisons, which could be only partly assigned to differences in decade of recruitment or type of chemotherapy regimen. We found considerable heterogeneity of treatment effects ($I^2 > 50\%$) for the outcomes OS and PFS only. Moderate heterogeneity (29%) was seen in SM treatment effects in the comparison RT vs. CRT.

Development of more effective (but also more carcinogenic) salvage treatment strategies over the decades will also have altered survival rates and SM risk after first-line treatment failure.

There may also be subgroups of patients within trials who benefit differently from different treatments. Concerning SM risk, we found no evidence of differences according to age or sex, but again, subgroup analyses are underpowered and might miss real differences. Further, many potential factors for SM risk, such as smoking habits, could not be analysed since data were not available.

We attempted to separate out the effects of first-line and salvage treatment by including an analysis of observation times censored at HD progression and relapse. However, this technique ignores all SM events caused by first-line treatment which occur after a progression/relapse. This censored analysis cannot therefore be regarded as conclusive evidence on comparative SM risk due to first-line treatment, but rather compares the risk of SM in periods of continuing complete remission. Tsodikov 1998 describes a better technique for simultaneously estimating SM risk due to first-line and salvage treatment.

Competing risks, in this case the risk of death from another cause, complicate the analysis of SM risk (Pepe 1993, Tai 2001). The results of standard Kaplan-Meier or Peto methods are valid only where the risk of competing events (other deaths) can be assumed independent of the risk of SM, which is implausible. Competing risks methods permit the construction of valid cumulative SM risk curves, but do not lend themselves to a test for differences between patient groups. Therefore, we have used competing risk cumulative incidence analysis, adapted to the Peto meta-analysis technique, as a sensitivity analysis to check whether the SM-free survival curves agree qualitatively with those of our main, standard analyses.

Other evidence

Progression-free and overall survival

The 3 previous meta-analyses (see above) have obtained similar results to ours with respect to OS and PFS.

RT vs. CRT

Both Shore 1990 and Specht 1998 found significantly better PFS with CRT than with RT alone in early stage patients (Shore: hazard ratio 0.303, $P < 0.01$; Specht: Peto odds ratio 0.47, $P < 0.00001$; present results for early stages: Peto odds ratio 0.49, $P < 0.0001$). However, these two meta-analyses failed to show a significant benefit in OS, whereas the present analysis demonstrates a significant and marked difference in OS for the early stages (POR = 0.71, $P < 0.0001$). The longer follow-up in the present analysis may explain the discrepant results.

CT vs. CRT

Loeffler 1998 showed improved PFS with CRT compared with the same CT in advanced stage patients (hazard ratio 0.63, $P < 0.001$; present results for advanced stages, unconfounded trials: POR = 0.75, $P = 0.02$), while, as in the present analysis, no difference in OS was found. Loeffler 1998 compared CRT to more chemotherapy alone (usually further cycles) and showed similar PFS in both arms (also seen in the present analysis) but better OS with CT alone (not confirmed in the present analysis).

IF-RT vs. EF-RT

Shore 1990 and Specht 1998 both demonstrated improved PFS with extended field in early stage patients (Shore: hazard ratio 0.671, $P < 0.01$; Specht: $POR = 0.637$, $P < 0.00001$). In the present analysis, significantly improved PFS was found for all stages together ($POR = 0.81$, $P = 0.009$) but the difference for the early stages alone was not significant ($POR = 0.88$, $P = 0.17$). No significant effect in OS was seen in any analysis.

Second malignancies

CT vs. CRT

The only previous meta-analytic result concerning SM risk was reported by Loeffler 1998: significantly more deaths due to secondary AL were observed with CRT compared with CT alone in predominantly advanced stage patients (hazard ratio 2.48, $P = 0.038$). If follow-up was censored at relapse, the results changed little (hazard ratio 2.79, $P = 0.042$). In the present analysis, concordant results were obtained ($POR = 1.82$, $P = 0.07$; censoring at progression/relapse: $POR = 2.75$, $P = 0.01$).

The main body of evidence concerning SM risk is provided by the numerous retrospective cohort and case-control studies described in Table 1, Table 2 and Table 3. The results, particularly concerning ST, vary considerably among these studies. Retrospective studies of SM vary in the methods used to classify treatment given. In most reports (including e.g. van Leeuwen 1994a, Swerdlow 1992, Kaldor 1992), treatment categories are based on both first-line and salvage treatment modalities. Some used the method of time-dependent covariates to allow for the effects of later treatments (e.g. Boivin 1988). A few studies regarded initial treatment only but censored at relapse (e.g. Biti 1994). Thus, such reports do not enable the overall SM risks associated with first-line treatment strategies to be compared directly. If progression/relapse rates as well as SM rates associated with salvage treatment are known, then overall SM risks can be calculated indirectly, but no such calculations were reported. The only exceptions were Dores 2002 and Ng 2002, in which the effect of initial treatment strategy on overall SM risk was investigated.

RT vs. CRT

Several previous studies reported higher SM (and AL, NHL and ST) risk with CRT than with RT alone. No study obtained higher risk with RT alone as in the present review. This presumably reflects the fact that the (many) patients relapsing after RT and receiving salvage CT were classified in the CRT group in most previous studies. The report by Ng 2002 also obtained a significantly higher relative risk of SM with initial CRT (6.1) than with initial RT alone (4.0; $P = 0.015$); however, this analysis included all stages IA-IVB and thus presumably two patient groups with greatly differing stage characteristics and treatment intensities were compared (RT alone predominantly stage I-IIIA, CRT all stages).

CT vs. CRT

A few studies showed higher risk with CRT than with CT alone (Abrahamsen 1993, Brusamolino 1998, van Leeuwen 1994a), but most found no difference. The present review also demonstrated a higher SM rate with CRT (in this comparison, progression/relapse rates are similar following both modalities).

CT vs. RT

Various studies demonstrated a higher SM or AL risk with CT than with RT. The present review, based on an inadequate number of patients, obtained a non-significant trend in this direction.

IF-RT vs. EF-RT

In a meta-analysis of more extensive against less extensive RT, Specht 1998 found no significant differences in SM risk between the two treatment groups with a trend to more SM with more extensive RT, in agreement with the present results.

Two studies (Ng 2002, Brusamolino 1998) reported a higher risk with EF than with IF radiotherapy. In the present review, the trend in this direction was not significant.

With two exceptions (Boivin 1995, Dores 2002), no significant differences between treatment modalities in the risk of all ST were observed, nor was a significant difference in NHL risk obtained (van Leeuwen 1994a reported a trend ($P = 0.06$) to more NHL with CRT than with CT or RT alone).

Using decision analysis methods, Hess 1994 calculated the overall AL risk associated with the choice of either RT alone or CRT for early/intermediate stage HD. The authors used relapse rates, salvage rates and AL rates after RT, CRT and salvage therapy as reported in the literature. Assuming relapse and salvage rates appropriate for stage IIB, and AL rates after RT, CRT and salvage of 0%, 6% and 10%, respectively, these authors calculated overall AL rates of 1.6% for initial RT and 5.4% for initial CRT. (In the present review, an odds ratio of 1.55 (more AL with CRT) was estimated ($P = 0.21$).) The decision analysis results are, however, sensitive to the assumed input values. A 6% AL rate after CRT may be appropriate for intensive MOPP therapy but not for modern chemotherapies. Replacing 6% by 1.5%, for instance, (other values unchanged) would equalise the overall rates with RT and CRT.

Effect sizes and trade-offs

Overall survival remains the single most important outcome for most Hodgkin lymphoma patients. Progression-free survival and second malignancies are analysed mainly as influential factors for OS. Ideally, quality of life would be recorded and compared in order to assess the quality as well as the length of life after diagnosis, but as yet, this outcome is not widely employed. Instead, acute toxicity, rate of progression/relapse and late toxicity (especially SM) are analysed as presumably the most important determinants of quality and length of life. Therefore, a treatment strategy which leads to better OS will in general be the treatment of choice; if OS does not differ between two treatments, then acute toxicity, PFS and SM should be considered. However, an individual patient may have his/her own priorities - for instance, for many older patients OS and SM will be less important than acute toxicity.

The primary aim of this review was to investigate second malignancies and thus help to fill an important gap in our knowledge. The SM results alone cannot determine the optimal treatment, and may play only a minor role. They must be put into the context of the OS and PFS results, as well as specific information on acute toxicities of a particular chemotherapy regimen and/or irradiation technique.

AUTHORS' CONCLUSIONS

Implications for practice

The main focus of the present review is second malignancies, since the authors consider that this important aspect lacks reliable evidence. SM alone can not, however, determine treatment policy, and in choosing the optimal treatment for a patient the physician must consider primarily overall and progression-free survival as

well as acute and late toxicity risk and quality of life. The present review summarises the evidence on OS, PFS and SM according to treatment modality and extent of radiotherapy. The acute toxicities associated with particular chemotherapy regimens and radiotherapy techniques are best documented in reports from the relevant trials.

The perceived optimal treatment for most patients with early stage Hodgkin's disease is currently between 2 and 6 cycles of an anthracyclin-containing polychemotherapy (predominantly ABVD) followed by radiotherapy of typically 30Gy to the involved or the extended field (Connors 2001, Diehl 2003, Kogel 2003, Meyer 2004). Stratification into two prognostic groups according to prognostic factors such as age, stage (I vs. II), B-symptoms, large mediastinal mass, bulky disease, number of involved nodes, extranodal lesions and/or erythrocyte sedimentation rate is widely practiced; patients with none of the considered risk factors receive fewer chemotherapy cycles or a milder regimen, or even radiotherapy alone (Mauch 1996a, Ng 1999).

The present results confirm the superiority of combined chemoradiotherapy for the majority of early stage patients. RT alone appears to be substantially inferior to CRT with respect to progression-free survival (up to 21% worse) and overall survival (up to 9% worse) as well as overall second malignancy risk (up to 9% worse). Likewise, CT alone appears to result in inferior OS (up to 12% worse) and PFS (up to 17% worse) compared with CRT (no significant difference in SM risk); however, this comparison is based on only 4 trials and 696 early stage patients. IF-RT seems to be as effective as EF-RT following chemotherapy; a tendency to more SM with EF-RT was observed, but this remains inconclusive. Therefore, a combination of CT with IF-RT seems to be the first-line treatment of choice for most early-stage patients with respect to all three outcomes OS, PFS and SM. Subgroup analyses suggest that the advantages of CRT are less for older patients. In the present review, detailed IPD concerning prognostic factors (see previous paragraph) were not collected: the possible deviation of certain subgroups from the above conclusions can not be investigated here.

For advanced stage patients, treatment with at least 6 cycles of an anthracyclin-containing chemotherapy, usually followed by involved field or extended field radiotherapy, is seen as optimal (Connors 2001, Diehl 2003, Kogel 2003, Meyer 2004). The present analysis confirms that progression-free survival is optimal with CRT compared with RT alone (up to 18% difference) or CT alone (up to 7% difference), but that the overall survival rate is not much influenced by the addition of radiotherapy to chemotherapy (95% confidence interval for hazard with CRT relative to CT: 0.83-1.12). SM risk appears to be lower with CT alone (a difference of 4% after 10-15 years). Therefore, the decision whether to administer additional radiotherapy after chemotherapy depends on weighing the risk of progression (favouring CRT) against the risk of second malignancy (favouring CT alone).

Implications for research

Assessment and comparison of second malignancy risk requires reliable long-term follow-up data from large numbers of patients, ideally those enrolled in randomised trials making the relevant treatment comparisons. In the present review, large numbers of patients, with long-term follow-up in some cases, were included. However, follow-up was incomplete in many trials, i.e., the date

of last information varied widely between patients in the trial. Methods for reporting of SM were not optimal in all trials, very few checked with a cancer registry, and for some trials the SM data may be seriously unreliable. Only 12 of 37 trials had a median follow-up of at least 20 years. Therefore, there is need for thorough follow-up of second malignancies over more than 20 years after first-line treatment in recent and future RCTs in Hodgkin's disease. Routine follow-up documentation should include questions concerning the occurrence, type and site of second malignancies. Update campaigns should aim to fill in missing information at particular time-points 20-30 years after the recruitment period. Where possible, trialists should collaborate with the relevant death and cancer registries in order to record mortality and SM as completely as possible.

Although the present analysis was able to detect significant differences in SM rates, the P values obtained were not small enough to confirm beyond reasonable doubt that the effects seen were not due to chance. Confidence intervals for relative SM risks are wide, so effect size is uncertain. An analysis with a larger number of person-years of observation is needed in order to produce more precise results concerning SM. Therefore, this review must be updated with longer follow-up from the included studies. Relevant trials which were too recent for inclusion in this review, as well as those published subsequently, should be included in an update. Some of the eligible trials for which data were unobtainable may provide data for the update.

The authors are convinced that previous SM analyses do not provide reliable evidence concerning the consequences of the choice of first-line treatment strategy for overall SM risk (see discussion). Most previous analyses have formed treatment groups according to all treatment ever received (first-line and salvage). This can be rectified by analysing the data according to first-line treatment only and never-the-less including follow-up and SM events after progression/relapse in the analysis. A further problem with such investigations remains, however, that the compared treatment groups were not randomly allocated and will differ with respect to various other factors (such as stage, age, prognostic factors) which may be correlated with SM risk. This problem can be minimised by careful use of multivariate regression techniques to account for the effects of these factors, but the reliability of a randomised comparison can not be attained.

The present results apply to broad categories of treatment but possibly not to particular treatments. In particular, many of the treatments included in the present review are outdated. It is important to note that the effectiveness of the first-line treatment (as measured by PFS) influences the amount of salvage treatment required and thus the overall SM risk. Furthermore, development of new salvage treatments may change the SM risk associated with the salvage and thus alter the overall SM risk.

Since it will never be possible to compare SM risk directly using randomised evidence for all comparisons of interest, other methods such as mathematical modelling, e.g. decision analysis as used by Hess 1994 and Ng 1999, are needed. The relevant parameters such as SM risk due to first-line treatment, progression/relapse rate, salvage rate and SM risk associated with salvage treatment must be estimated (e.g. using relevant published studies) and inserted into the model. The effect of different combinations of first-line and salvage therapy and of variations in the input parameters can be explored.

Individual RCTs will probably remain too small to provide reliable comparisons of SM risk. Meta-analysis is required in order to make randomised comparisons with large enough numbers of patients and person-years of observation. An update of the present review should if possible be restricted to trials using chemotherapy regimens containing an anthracyclin (such as doxorubicin) and preferably avoiding alkylating agents. Ideally, further data on prognostic factors (e.g. large mediastinal mass, bulky disease, number of involved nodes, extranodal lesions and erythrocyte sedimentation rate for early stages; haemoglobin, serum albumin, leukocyte count, lymphocyte count ([Hasenclever 1998](#)) for advanced stages) should be collected and the relevant subgroup analyses performed.

Since the choice of chemotherapy regimen seems to be critical for all relevant outcomes including second malignancies, a systematic review comparing the effects of different CT regimens on SM risk is required. The authors have searched for and classified the relevant RCTs comparing two or more regimens. Adequate numbers of trials and patients were found for comparisons between MOPP, ABVD and MOPP/ABVD or closely similar regimens. Thus, the authors will perform and submit a Cochrane review concerning these comparisons, analogous to the present review, assuming that sufficient IPD can be acquired from trialists.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

CALGB 6604

Methods	CT vs. CT + IF vs. CT + EF and RT vs. CRT; unconfounded; late randomisation; 1966 to 1971; multicenter
Participants	107 (CT: 22, CT + IF: 24, CT + EF: 21, RT: 18, CRT: 22) + 16 not evaluated patients; stage III
Interventions	CT: Vinblastine + Mechlorethamine; EF: TNI; RT: TNI
Outcomes	DFS, OS
Notes	Data of not evaluated patients were not submitted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

CALGB 7451

Methods	CT vs. CRT vs. RT; unconfounded; 1974 to 1981; multicenter
Participants	233 (CT: 63, CRT: 115, RT: 53, arm unknown: 2); stage III
Interventions	CT: 6 x BOPP (+maintenance); RT: TNI
Outcomes	CR rate, DFS, OS
Notes	2 patients with unknown arm not included

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

CALGB 7551

Methods	CT vs. CRT; partly confounded; 1975 to 1982; multicenter
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CALGB 7551 (Continued)

Participants	337 (CT: 167, CRT: 169; arm unknown: 1)
Interventions	CT: CVPP (6 or 12); RT: IF (adjuvant or sandwich)
Outcomes	CR-rate, DFS, OS
Notes	29 patients excluded because of erroneous HD-diagnosis; 1 patient excluded because arm unknown.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

CALGB 7751

Methods	CT vs. CRT; unconfounded; 1977 to 1983; multicenter
Participants	75 (CT: 35, CRT: 37, arm unknown: 3); unfavourable stages I to II
Interventions	CT: 6 x CVPP; RT: IF or EF
Outcomes	CR-rate, DFS, OS
Notes	11 patients excluded because of erroneous HD-diagnosis; 3 patients excluded because arm unknown.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

EORTC, #20884

Methods	CT vs. CRT; unconfounded; 1989 to 2000; multicenter; late randomisation
Participants	333 (CT: 161, CRT: 172); stages III to IV; age 15 to 70
Interventions	CT: MOPP/ABV (6 or 8); RT: IF
Outcomes	OS, RFS, EFS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

EORTC, H5U

Methods	RT vs. CRT; confounded; 1977 to 1982; multicenter
Participants	296 (RT: 152; CT: 144); unfavourable stages I to II
Interventions	RT: (S)TNI; CRT: 3 x MOPP + Mantle-RT + 3 x MOPP
Outcomes	OS, RFS, FFP, treatment related deaths, SM related deaths
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

EORTC, H7F

Methods	RT vs. CRT; confounded; 1988 to 1993; multicenter
Participants	333 (RT: 165, CRT: 168); favourable stages I to II
Interventions	RT: STNI; CRT: 6 x EBVP + IF
Outcomes	OS, EFS, relapse- and death-rates, SM-rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

EORTC-GELA, H8F

Methods	RT vs. CRT; confounded; 1993 to 1998; multicenter
Participants	543 (RT: 273, CRT: 270); favourable stages I to II
Interventions	RT: STNI; CRT: 3 x MOPP/ABV+IF
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

EORTC-GELA, H8U

Methods	CT + IF vs. CT + EF; partly confounded; 1993 to 1999; multicenter
Participants	996 (6 CT + IF: 336, 4 CT + IF: 333, 4 CT + EF: 327); unfavourable stages I to II
Interventions	CT: MOPP/ABV (4 or 6)
Outcomes	OS, FFTF, response rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

GATLA 9-H-77

Methods	CT vs. CRT; unconfounded; 1977 to 1986; multi-centre
Participants	479 patients (CT: 249, CRT: 228, arm unknown: 2); stages I to IV. Study closed for stages IIIB to IV in 1979, however 32 such patients were randomised after 1979 and included in the data. 1977 to 1979: stages I to IV 1979 to 1986: stages I to IIIA, no prior HD treatment
Interventions	CT: 6 x CVPP; RT: IF (sandwich)
Outcomes	DFS, OS, FFTF
Notes	6 patients excluded due to missing arm, missing date of randomisation, or erroneous HD diagnosis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

GELA H89

Methods	CT vs. CRT; confounded; 1989 to 1996; multicenter; late randomisation
Participants	419 patients (CT: 208, CRT: 211); stages IIIB to IV, age 15 to 65
Interventions	CT: 8 x MOPP/ABV or 8 x ABVPP; RT: (S)TNI
Outcomes	CR-rate after 4 x CT, 6 x CT, completion of treatment, DFS, EFS, OS
Notes	

Risk of bias

GELA H89 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

GHSg, HD3

Methods	CT vs. CRT; confounded; 1982 to 1988; multicenter; late randomisation	
Participants	100 patients (CT: 49, CRT: 51); stages IIIB to IV; age 15 to 60	
Interventions	CT: 4 (COPP + ABVD); CRT: 3 (COPP + ABVD) + IF-RT	
Outcomes	CR-rate, FFTF, OS	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

GHSg, HD7

Methods	RT vs. CRT; unconfounded; 1994 to 1998; multi-centre	
Participants	627 patients (RT: 311, CRT: 316); favourable stages I to II	
Interventions	RT: EF; CT: 2 x ABVD	
Outcomes	CR-rate, FFTF, OS	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

GHSg, HD8

Methods	CT + IF vs. CT + EF; unconfounded; 1993 to 1998; multi-centre	
Participants	1136 patients (IF: 571, EF: 565); unfavourable stages I to II, favourable stage IIIA	
Interventions	CT: 2 x (COPP + ABVD)	
Outcomes	OS, FFTF, CR, progression, relapse and SM rates	

GHSg, HD8 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

GPMC, EF-RT vs. IF-R

Methods	CT + IF vs. CT + EF; unconfounded; 1976 to 1981; multi-centre; late randomisation
Participants	90 patients (IF: 43, EF: 47); stages I to IIIA; age 15 to 70
Interventions	CT: 3 x MOPP (+ 3 x MOPP after RT for unfavourable patients) EF: 3 x MOPP x 3+ EF-RT (+ 3 x MOPP for unfavourable groups after RT)
Outcomes	OS, DFS, CR rate after 3MOPP, after RT, after additional 3 MOPP
Notes	Only one institution provided data; therefore 245 patients could not be included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lygra I

Methods	IF-RT vs. EF-RT; 1969 to 1971; multi-centre
Participants	50 patients (IF: 19, EF: 31); stages I to II
Interventions	IF-RT vs. EF-RT
Outcomes	RFS, OS
Notes	It was necessary to 'rescue' and reinclude patients assigned to each treatment arm who had apparently been deleted from the lists kept by the trialists at that time.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lygra II

Methods	RT vs. CRT; confounded; 1971 to 1985; multi-centre
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Lygra II (Continued)

Participants	327 patients (RT: 164, CRT: 163); stages I to II supradiaphragmatic disease, no stage E	
Interventions	RT: (S)TNI ; CRT: Mantle-RT+ 6 x MOPP	
Outcomes	RFS, relapse site, OS	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Manchester, HD 1

Methods	RT vs. CRT; unconfounded; 1974 to 1981; single centre	
Participants	115 patients (RT: 56, CRT: 59); stages I to II without bulky mediastinal disease; age 16 to 65	
Interventions	RT: Mantle; CT: adjuvant MVPP	
Outcomes	FFP, OS, death and progression rates, causes of death, SM	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Manchester, HD 2

Methods	CT vs. CRT; unconfounded; 1975 to 1984; single centre	
Participants	65 patients (CT: 31, CRT: 34); stage IIIA	
Interventions	CT: MVPP(6-10); RT: IF	
Outcomes	FFP, OS, death and progression rates, causes of death, SM	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Manchester, RT v. CRT

Methods	RT vs. CRT; unconfounded; 1989 to 1997; single centre
Participants	125 patients (RT: 63; CRT: 62); stages IA, IIA; no mediastinal bulk
Interventions	RT: IF-RT; CT: 4 weeks VAPEC-B before IF-RT
Outcomes	OS, FFP, rates of death and progression, second malignancies
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Mexico, 82H031

Methods	CT vs. RT vs. CRT; unconfounded; 1983 to 1988; single-centre
Participants	307 patients (RT: 106, CT: 99, CRT: 102); stages I-II supradiaphragmatic disease and bulky disease
Interventions	CT: 6 x ABVD; RT: Mantle-RT; CRT: sandwich
Outcomes	CR-rates, OS, DFS, SM
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Milan, trial # 9005

Methods	CT + IF vs. CT + EF; unconfounded; 1990 to 1996; single-centre
Participants	140 patients (IF: 72, EF: 68); stages I to IIA; age 16 to 70
Interventions	CT: 4 x ABVD; EF: STNI
Outcomes	OS, FFP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

MSKCC, trial # 90-44

Methods	CT vs. CRT, unconfounded; 1990 to 2000; single-centre
Participants	152 (CT: 76, CRT: 76); favourable stages I to II A/B, IIIA
Interventions	CT: 6 x ABVD; RT: EF-RT (until 1999) and IF-RT (1999-2000)
Outcomes	OS, DFS, FFP
Notes	11 patients were excluded because of erroneous HD diagnosis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

NCI Canada, HD1

Methods	CT vs. CRT, unconfounded; 1972 to 1976; multi-centre; late randomisation
Participants	82 (CT: 28, CRT: 54); stages IIIB, IVA/B; age 16 to 70
Interventions	CT: 6 x MOPP; RT: EF-RT (abdomen+mantle)
Outcomes	CR-rate after 3 x CT/ 6 x CT, time to death with HD, FFS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Obninsk, advanced

Methods	CT vs. CT + RT, partly confounded and CT + IF vs. CT + EF, unconfounded; 1974 to 1981; single-centre
Participants	284 (CT: 84, CT + IF: 87, CT + EF: 113); stages II(XE) - IV
Interventions	CT: COPP (2-12)
Outcomes	disease specific survival
Notes	Randomisation rates during the various years of recruitment were not always balanced between treatment arms.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Obninsk, advanced (Continued)

Allocation concealment?	Unclear risk	B - Unclear
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Obninsk, R 18

Methods	CT + IF vs. CT + EF; partly confounded; 1977 to 1983; single-centre; late randomisation
Participants	237 (IF: 78, EF: 159) stages I to II
Interventions	CT: 1 x COPP + 3x (5 x) COPP after RT
Outcomes	OS, DFS, incidence of relapses
Notes	Randomisation method using date of birth; however, the data did not agree with the method stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Rome, Florence, 1979

Methods	RT vs. CT; 1979 to 1982; multi-centre
Participants	94 (RT: 48, CT: 46); stages I to IIA
Interventions	CT: 6 x MOPP; RT: MF-RT + lumbar bar
Outcomes	CR-rates; OS; RFS; FFP; SM rates
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Rome, HD 94

Methods	IF-RT vs. EF-RT; unconfounded; 1993 to 1995; single-centre; late randomisation
Participants	130 (IF: 63, EF: 67); unfavourable stage II, favourable stage IIIA; age 16 to 74
Interventions	EF: STNI; CT: 4 x ABVD
Outcomes	CR, OS, RFS, EFS
Notes	79 patients could not be included because data were not obtained.

Rome, HD 94 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Rome, RT vs. CRT

Methods	RT vs. CRT, unconfounded; 1983 to 1993; single-centre
Participants	103 (RT: 48, CRT: 55); stage IIA (supradiaphragmatic HD and positive mediastinal localization; mediastinal mass less than one third of the maximum thorax diameter)
Interventions	RT: STNI; CT: 1 x ABVD
Outcomes	OS, RFS, SM rates
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

SJCRH, HD study II B

Methods	RT vs. CRT, unconfounded; 1972 to 1975; single-centre
Participants	24 (RT: 13, CRT: 11); stages IIA, IIIA; age <= 22
Interventions	RT: EF; CT: VCP
Outcomes	CR-rate, RFS, OS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

SJCRH, HD Study IIC

Methods	CT vs. CRT, unconfounded; 1972 to 1975; single-centre
Participants	24 (CT: 13, CRT: 11); stages IIB, IIIB, IV; age <= 22yrs
Interventions	CT: VCPP; RT: EF

SJCRH, HD Study IIC (Continued)

Outcomes CR-rate, RFS, OS

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Stanf. C1-C3, G1

Methods RT vs. CRT, confounded; 1980 to 1995; single-centre

Participants 106 (RT: 57, CRT: 49); stages I to IIIA (patients with large mediastinal masses and patients with multiple extralymphatic (E) lesions were excluded)

Interventions RT: (S)TLI; CRT: IF-RT + 6 x VBM

Outcomes FFP, OS

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Stanf. C7-10, C12-15

Methods CT vs. CRT, confounded; 1980 to 1987; single-centre

Participants 74 (CT: 40; CRT: 34); stages IIIA to IV

Interventions CT: 6 x (MOPP+ABVD) or 6 x (PAVe+ABVD)
CRT: 3 x (2 x PAVe + TLI)

Outcomes FFP, OS

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Stanf. H1, L1, L2

Methods	IF-RT vs. EF-RT, 1962 to 1970; single-centre
Participants	209 (IF: 87; EF:1 22); stages I to III
Interventions	EF: TLI or limited EF
Outcomes	FFP, OS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Stanf. K7, S8

Methods	CT vs. CRT, unconfounded; 1969 to 1980; single-centre
Participants	58 (CT: 28; CRT: 30); stage IV; S8: age > 15
Interventions	CT: 6 x MOPP; CRT: alternating/split TLI + MOP(P)
Outcomes	OS, FFP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Stanf. S1

Methods	RT vs. CRT, confounded; 1974 to 1980; single-centre
Participants	71 (RT: 35; CRT: 36); stages IA, IIA; age>15
Interventions	RT: STNI; CRT: IF-RT + 6 x MOP(P)
Outcomes	OS, FFP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Stanf.H2-H6, K1, R1

Methods	RT vs. CRT, unconfounded; 1968 to 1979; single-centre
Participants	269 (RT: 141; CRT: 128); stages I to IV
Interventions	RT: (S)TLI or Mantle or inverted Y CT: 6 x MOPP
Outcomes	OS, FFP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
BNLI, IF vs. EF	IPD not contributed. IF vs. EF, 603 patients
BNLI, RT vs. CRT	IPD not contributed. RT vs. CRT, unconfounded RT = TNI; CT = LOPP 85 patients
BNLI, RT vs. CT	IPD not contributed. RT vs. CT RT = TNI; CT = 6 x MOPP 165 patients
Can-Am RHDG	Database destroyed. IF vs. EF 460 patients
CCG, #521	IPD not contributed. CT vs. CRT, confounded CT = 6 x MOPP/ABVD; CRT = 6 x ABVD+IF-RT 111 patients
CCG, #5942	IPD not contributed. CT vs. CRT, unconfounded CT = COPP/ABV hybr.; RT = IF (low dose) 501 patients
Chicago, RT vs. CRT	Data could not be located. RT vs. CRT, unconfounded. RT = EF; CT = COPP 49 patients

Study	Reason for exclusion
ECOG, 2475	IPD not contributed. RT vs. CRT, confounded RT = EF; CRT = C/MOPP+IF 34 patients
ECOG, EST 1476	IPD not contributed. CT vs. CRT, confounded CT = 6 x Bleo-MOPP + 3 x ABVD; CRT = 6 x Bleo-MOPP + IF-RT 232 patients
ECOG, EST 1481	IPD not contributed. CT vs. CRT, partly confounded CT = BCVPP vs. MOPP/ABVD; CRT = BCVPP + IF(low dose) 319 patients
GEMH, H7701	Data no longer available. Information Dr. Andrieu. IF vs. EF, plus CT 79 patients
GEMH, H9 69	Data no longer available. Information Dr. Andrieu. RT vs. CRT CT = MOPP 198 patients
IHDCS (POG)	IPD not contributed. RT vs. CRT, partly confounded RT = IF or EF; CRT = IF + MOPP 220 patients
Lygra III	Few or no patients recruited; study abandoned. Information Dr. Specht September 2003. RT vs. CRT vs. CT
Lyon, LMS 80a	IPD not contributed. RT vs. CRT, confounded RT = EF; CRT = 6 x MOPP + IF 48 patients, stage IIIa
Lyon, LMS 80b	IPD not contributed. CT vs. CRT, confounded CT = 12 x MOPP/CVPP; CRT = 3 x MOPP + MF-RT + 3 x MOPP + inverted Y 58 patients, stage IIIb
Mexico Ho 8326	No cases of SM documented. CT vs. CRT, unconfounded CT = 6 x EBVD; RT = IF 118 patients
Moscow	No contact to trialists established. RT vs. CRT, partly confounded RT = EF; CRT = 2 x (or 3 x) CVPP + IF (or EF) + 2 x (or 3 x) CVPP 95 patients
NCI, CT vs. CRT	IPD not contributed. CT vs. CRT, unconfounded RT = EF; CT = 6 x MOPP 36 patients

Study	Reason for exclusion
NCI, RT vs. CRT	IPD not contributed. RT vs. CRT, unconfounded RT = EF; CT = 6 x MOPP 87 patients
NCI, RT vs. CT	IPD not contributed. RT vs. CT RT = EF; CT = 6 x MOPP 86 patients
POG, #8625	IPD not contributed CT vs. CRT, confounded CT = 3 x MOPP/ABVD; CRT = 2 x MOPP/ABVD + IF 247 patients
POG, #8725	IPD not contributed. CT vs. CRT, unconfounded CT = 4 x MOPP/ABVD; RT = low-dose TNI 181 patients
Roswell Park	No contact to trialists established. RT vs. CRT, unconfounded RT = IF or TNI; CT = ChlVPP 165 patients
St. Bartholomew's	No contact to trialists established. RT vs. CT RT = TNI, CT = 6 x MVPP 40 patients
SWOG #7518	IPD not contributed. CT vs. CRT, confounded CT = 10 x MOPP-Bleo; CRT = 3 x MOPP-Bleo + TNI 118 patients
SWOG #774/775	IPD not contributed. CT vs. CRT, unconfounded (MOPP vs. MOPP/BLEO) + (MOPP vs. IF-RT + MOPP) 254 patients
SWOG #7808	IPD not contributed. CT vs. CRT, unconfounded CT = 6 x MOPP-BAP; RT = low-dose IF-RT 278 patients
SWOG #781	IPD not contributed. RT vs. CRT, confounded RT = EF; CRT = IF-RT + 6 x MOPP 235 patients
SWOG #9133	IPD not contributed. RT vs. CRT, unconfounded RT = STLI; CT = 3 x (doxorubicin + vinblastine) 348 patients
Western CSG #135	IPD not contributed. RT vs. CRT, unconfounded RT = TNI; CT = MOPP

Study	Reason for exclusion
	40 patients

DATA AND ANALYSES

Comparison 1. RT vs. CT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 overall survival	3	415	Peto Odds Ratio (99% CI)	1.17 [0.85, 1.62]
1.1 early stages	2	299	Peto Odds Ratio (99% CI)	1.03 [0.69, 1.52]
1.2 advanced stages	1	116	Peto Odds Ratio (99% CI)	1.52 [0.87, 2.66]
2 OS - early stages - sex	2	299	Peto Odds Ratio (99% CI)	0.99 [0.67, 1.47]
2.1 female	2	165	Peto Odds Ratio (99% CI)	0.78 [0.45, 1.35]
2.2 male	2	134	Peto Odds Ratio (99% CI)	1.27 [0.72, 2.25]
3 OS - advanced stages - sex	1	115	Peto Odds Ratio (99% CI)	1.54 [0.88, 2.70]
3.1 female	1	47	Peto Odds Ratio (99% CI)	1.65 [0.65, 4.19]
3.2 male	1	68	Peto Odds Ratio (99% CI)	1.49 [0.74, 2.98]
4 progression free survival	3	415	Peto Odds Ratio (99% CI)	0.99 [0.74, 1.32]
4.1 early stages	2	299	Peto Odds Ratio (99% CI)	0.97 [0.69, 1.37]
4.2 advanced stages	1	116	Peto Odds Ratio (99% CI)	1.03 [0.61, 1.73]
5 PFS - censored at cut-off date	3	415	Peto Odds Ratio (99% CI)	1.00 [0.75, 1.34]
5.1 early stages	2	299	Peto Odds Ratio (99% CI)	0.99 [0.69, 1.40]
5.2 advanced stages	1	116	Peto Odds Ratio (99% CI)	1.04 [0.61, 1.76]
6 PFS - early stages - sex	2	299	Peto Odds Ratio (99% CI)	0.96 [0.68, 1.36]
6.1 female	2	165	Peto Odds Ratio (99% CI)	0.66 [0.40, 1.07]
6.2 male	2	134	Peto Odds Ratio (99% CI)	1.43 [0.87, 2.36]
7 PFS - advanced stages - sex	1	115	Peto Odds Ratio (99% CI)	1.02 [0.60, 1.71]
7.1 female	1	47	Peto Odds Ratio (99% CI)	1.01 [0.44, 2.31]
7.2 male	1	68	Peto Odds Ratio (99% CI)	1.02 [0.52, 2.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 second malignancy free survival	3	415	Peto Odds Ratio (99% CI)	2.12 [0.81, 5.55]
8.1 early stages	2	299	Peto Odds Ratio (99% CI)	3.37 [1.01, 11.20]
8.2 advanced stages	1	116	Peto Odds Ratio (99% CI)	0.92 [0.18, 4.62]
9 SM before progression/relapse	3	415	Peto Odds Ratio (99% CI)	1.99 [0.54, 7.37]
9.1 early stages	2	299	Peto Odds Ratio (99% CI)	4.02 [0.70, 23.22]
9.2 advanced stages	1	116	Peto Odds Ratio (99% CI)	0.82 [0.11, 5.86]
10 SM free survival - early stages - sex	2	299	Peto Odds Ratio (99% CI)	3.12 [0.91, 10.67]
10.1 female	2	165	Peto Odds Ratio (99% CI)	4.63 [0.60, 35.73]
10.2 male	2	134	Peto Odds Ratio (99% CI)	2.49 [0.53, 11.63]
11 SM free survival - advanced stages - sex	1	115	Peto Odds Ratio (99% CI)	0.87 [0.17, 4.35]
11.1 female	1	47	Peto Odds Ratio (99% CI)	0.44 [0.04, 4.28]
11.2 male	1	68	Peto Odds Ratio (99% CI)	1.72 [0.18, 16.76]

Analysis 1.1. Comparison 1 RT vs. CT, Outcome 1 overall survival.

Study or subgroup	RT n/N	CT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Test for overall effect: $Z=0.96$ ($P=0.34$)					
Test for subgroup differences: $\text{Chi}^2=1.28$, $\text{df}=1$ ($P=0.26$), $I^2=22.07\%$					
<div style="display: flex; justify-content: space-between;"> Favours CT 0.1 0.2 0.5 1 2 5 10 Favours RT </div>					

Analysis 1.2. Comparison 1 RT vs. CT, Outcome 2 OS - early stages - sex.

Study or subgroup	RT n/N	CT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
1.2.1 female					
Mexico, 82HO31	28/56	23/59		44.09%	0.7[0.32,1.52]
Rome, Florence, 1979	5/29	4/21		8.12%	1.48[0.24,9.13]
Subtotal (95% CI)	85	80		52.21%	0.78[0.45,1.35]
Total events: 33 (RT), 27 (CT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=0.96$, $\text{df}=1$ ($P=0.33$); $I^2=0\%$					
Test for overall effect: $Z=0.88$ ($P=0.38$)					
1.2.2 male					
Mexico, 82HO31	23/50	20/40		34.15%	1.21[0.5,2.95]
Rome, Florence, 1979	6/19	9/25		13.64%	1.43[0.35,5.84]
Subtotal (95% CI)	69	65		47.79%	1.27[0.72,2.25]
Total events: 29 (RT), 29 (CT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=0.07$, $\text{df}=1$ ($P=0.8$); $I^2=0\%$					
Test for overall effect: $Z=0.83$ ($P=0.41$)					
Total (95% CI)	154	145		100%	0.99[0.67,1.47]
Total events: 62 (RT), 56 (CT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=2.48$, $\text{df}=3$ ($P=0.48$); $I^2=0\%$					
Test for overall effect: $Z=0.06$ ($P=0.95$)					
Test for subgroup differences: $\text{Chi}^2=1.46$, $\text{df}=1$ ($P=0.23$), $I^2=31.39\%$					
<div style="display: flex; justify-content: space-between;"> Favours CT 0.1 0.2 0.5 1 2 5 10 Favours RT </div>					

Analysis 1.3. Comparison 1 RT vs. CT, Outcome 3 OS - advanced stages - sex.

Study or subgroup	RT n/N	CT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
1.3.1 female					
CALGB 7451	6/20	13/27		35.82%	1.65[0.48,5.61]
Subtotal (95% CI)	20	27		35.82%	1.65[0.65,4.19]
Total events: 6 (RT), 13 (CT)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=1.05$ ($P=0.29$)					
1.3.2 male					
CALGB 7451	14/32	21/36		64.18%	1.49[0.6,3.71]
Subtotal (95% CI)	32	36		64.18%	1.49[0.74,2.98]
Total events: 14 (RT), 21 (CT)					
Heterogeneity: Not applicable					
<div style="display: flex; justify-content: space-between;"> Favours CT 0.1 0.2 0.5 1 2 5 10 Favours RT </div>

Analysis 1.4. Comparison 1 RT vs. CT, Outcome 4 progression free survival.

Analysis 1.5. Comparison 1 RT vs. CT, Outcome 5 PFS - censored at cut-off date.

Analysis 1.6. Comparison 1 RT vs. CT, Outcome 6 PFS - early stages - sex.

Analysis 1.7. Comparison 1 RT vs. CT, Outcome 7 PFS - advanced stages - sex.

Analysis 1.8. Comparison 1 RT vs. CT, Outcome 8 second malignancy free survival.

Analysis 1.9. Comparison 1 RT vs. CT, Outcome 9 SM before progression/relapse.

Analysis 1.10. Comparison 1 RT vs. CT, Outcome 10 SM free survival - early stages - sex.

Analysis 1.11. Comparison 1 RT vs. CT, Outcome 11 SM free survival - advanced stages - sex.

Comparison 2. CT v CRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 overall survival	16	2861	Peto Odds Ratio (99% CI)	0.90 [0.78, 1.03]
1.1 advanced stages	13	2165	Peto Odds Ratio (99% CI)	0.96 [0.83, 1.12]
1.2 early stages	4	696	Peto Odds Ratio (99% CI)	0.62 [0.44, 0.88]
2 OS - unconfounded trials	10	1570	Peto Odds Ratio (99% CI)	0.83 [0.68, 1.01]
2.1 early stages	4	696	Peto Odds Ratio (99% CI)	0.62 [0.44, 0.88]
2.2 advanced stages	7	874	Peto Odds Ratio (99% CI)	0.95 [0.75, 1.21]
3 OS - early stages - sex	4	696	Peto Odds Ratio (99% CI)	0.63 [0.45, 0.88]
3.1 male	4	393	Peto Odds Ratio (99% CI)	0.56 [0.36, 0.87]
3.2 female	4	303	Peto Odds Ratio (99% CI)	0.74 [0.45, 1.22]
4 OS - advanced stages - sex	13	2165	Peto Odds Ratio (99% CI)	0.95 [0.82, 1.10]
4.3 male	13	1394	Peto Odds Ratio (99% CI)	0.90 [0.75, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 female	13	771	Peto Odds Ratio (99% CI)	1.07 [0.82, 1.40]
5 OS- early stages - age	4	697	Peto Odds Ratio (99% CI)	0.56 [0.40, 0.80]
5.1 0-15 years	1	131	Peto Odds Ratio (99% CI)	1.07 [0.33, 3.42]
5.2 16-39 years	4	386	Peto Odds Ratio (99% CI)	0.42 [0.27, 0.66]
5.3 age 40+	4	180	Peto Odds Ratio (99% CI)	0.85 [0.45, 1.61]
6 OS - advanced stages - age	13	2162	Peto Odds Ratio (99% CI)	0.96 [0.82, 1.12]
6.1 0-15 years	10	105	Peto Odds Ratio (99% CI)	0.77 [0.37, 1.56]
6.2 16-39 years	13	1375	Peto Odds Ratio (99% CI)	0.87 [0.71, 1.08]
6.3 40-59 years	12	508	Peto Odds Ratio (99% CI)	1.15 [0.88, 1.52]
6.4 60 years and older	9	174	Peto Odds Ratio (99% CI)	0.98 [0.63, 1.53]
7 OS - early stages - type of RT	4	684	Peto Odds Ratio (99% CI)	0.62 [0.44, 0.87]
7.1 CT vs. CT+IF-RT	2	354	Peto Odds Ratio (99% CI)	1.06 [0.65, 1.70]
7.2 CT vs. CT + EF-RT	2	330	Peto Odds Ratio (99% CI)	0.36 [0.22, 0.59]
8 OS - advanced stages - type of RT	13	2271	Peto Odds Ratio (99% CI)	0.93 [0.81, 1.07]
8.1 CT vs. CT + IF-RT	7	1169	Peto Odds Ratio (99% CI)	0.99 [0.82, 1.20]
8.2 CT vs. CT + EF-RT	8	1102	Peto Odds Ratio (99% CI)	0.86 [0.70, 1.06]
9 PFS confounded advanced	6	1291	Peto Odds Ratio (95% CI)	0.87 [0.73, 1.04]
9.1 advanced stages	6	1291	Peto Odds Ratio (95% CI)	0.87 [0.73, 1.04]
10 progression free survival	16	2857	Peto Odds Ratio (99% CI)	0.77 [0.68, 0.87]
10.1 early stages	4	692	Peto Odds Ratio (99% CI)	0.60 [0.46, 0.78]
10.2 advanced stages	13	2165	Peto Odds Ratio (99% CI)	0.83 [0.72, 0.95]
11 PFS - censored at cut-off date	16	2857	Peto Odds Ratio (99% CI)	0.76 [0.67, 0.86]
11.1 early stages	4	692	Peto Odds Ratio (99% CI)	0.57 [0.43, 0.75]
11.2 advanced stages	13	2165	Peto Odds Ratio (99% CI)	0.82 [0.71, 0.95]
12 PFS - unconfounded trials only	10	1566	Peto Odds Ratio (99% CI)	0.68 [0.57, 0.81]
12.1 early stages	4	692	Peto Odds Ratio (99% CI)	0.60 [0.46, 0.78]
12.2 advanced stages	7	874	Peto Odds Ratio (99% CI)	0.75 [0.60, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 PFS - early stages - sex	4	692	Peto Odds Ratio (99% CI)	0.58 [0.44, 0.75]
13.1 female	4	302	Peto Odds Ratio (99% CI)	0.60 [0.40, 0.90]
13.2 male	4	390	Peto Odds Ratio (99% CI)	0.56 [0.39, 0.79]
14 PFS - advanced stages - sex	13	2165	Peto Odds Ratio (99% CI)	0.82 [0.72, 0.95]
14.1 female	13	771	Peto Odds Ratio (99% CI)	0.81 [0.64, 1.04]
14.2 male	13	1394	Peto Odds Ratio (99% CI)	0.83 [0.70, 0.99]
15 PFS - early stages - age	4	690	Peto Odds Ratio (99% CI)	0.56 [0.42, 0.73]
15.1 0-15 years	1	130	Peto Odds Ratio (99% CI)	0.88 [0.46, 1.68]
15.2 16-39 years	4	385	Peto Odds Ratio (99% CI)	0.41 [0.29, 0.58]
15.3 age 40+	4	175	Peto Odds Ratio (99% CI)	0.79 [0.47, 1.35]
16 PFS - advanced stages - age	13	2162	Peto Odds Ratio (99% CI)	0.83 [0.72, 0.96]
16.1 0-15 years	10	105	Peto Odds Ratio (99% CI)	0.62 [0.33, 1.14]
16.2 16-39 years	13	1375	Peto Odds Ratio (99% CI)	0.73 [0.60, 0.88]
16.3 40-59 years	12	508	Peto Odds Ratio (99% CI)	1.00 [0.76, 1.31]
16.4 60 years and older	9	174	Peto Odds Ratio (99% CI)	1.25 [0.78, 2.00]
17 second malignancy free survival	16	2861	Peto Odds Ratio (99% CI)	1.38 [1.00, 1.89]
17.1 early stages	4	696	Peto Odds Ratio (99% CI)	1.17 [0.48, 2.83]
17.2 advanced stages	13	2165	Peto Odds Ratio (99% CI)	1.41 [1.00, 1.98]
18 SM free survival - censored at cut-off date	16	2861	Peto Odds Ratio (99% CI)	1.71 [1.16, 2.53]
18.1 early stages	4	696	Peto Odds Ratio (99% CI)	1.85 [0.59, 5.83]
18.2 advanced stages	13	2165	Peto Odds Ratio (99% CI)	1.69 [1.12, 2.56]
19 SM free survival - unconfounded trials only	10	1570	Peto Odds Ratio (99% CI)	1.27 [0.82, 1.98]
19.1 early stages	4	696	Peto Odds Ratio (99% CI)	1.17 [0.48, 2.83]
19.2 advanced stages	7	874	Peto Odds Ratio (99% CI)	1.31 [0.79, 2.18]
20 SM free survival - confounded trials only	5	988	Peto Odds Ratio (99% CI)	1.47 [0.88, 2.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.2 advanced stages	5	988	Peto Odds Ratio (99% CI)	1.47 [0.88, 2.46]
21 SM before progression or relapse	16	2857	Peto Odds Ratio (99% CI)	1.60 [1.10, 2.33]
21.1 early stages	4	692	Peto Odds Ratio (99% CI)	0.98 [0.37, 2.56]
21.2 advanced stages	13	2165	Peto Odds Ratio (99% CI)	1.75 [1.17, 2.63]
22 SM free survival - early stages - sex	4	696	Peto Odds Ratio (99% CI)	1.24 [0.50, 3.04]
22.1 female	4	303	Peto Odds Ratio (99% CI)	1.70 [0.41, 7.11]
22.2 male	4	393	Peto Odds Ratio (99% CI)	1.01 [0.32, 3.19]
23 SM free survival - advanced stages - sex	13	2165	Peto Odds Ratio (99% CI)	1.41 [1.00, 1.99]
23.1 female	13	771	Peto Odds Ratio (99% CI)	2.08 [1.14, 3.80]
23.2 male	13	1394	Peto Odds Ratio (99% CI)	1.18 [0.77, 1.78]
24 SM free survival - early stages - age	4	563	Peto Odds Ratio (99% CI)	0.97 [0.38, 2.44]
24.1 16-39 years	4	386	Peto Odds Ratio (99% CI)	1.64 [0.46, 5.85]
24.2 age 40+	4	177	Peto Odds Ratio (99% CI)	0.54 [0.14, 2.07]
25 SM free survival - advanced stages - age	13	2162	Peto Odds Ratio (99% CI)	1.49 [1.05, 2.12]
25.1 0-15 years	10	105	Peto Odds Ratio (99% CI)	0.52 [0.13, 2.18]
25.2 16-39 years	13	1375	Peto Odds Ratio (99% CI)	1.77 [1.01, 3.10]
25.3 40-59 years	12	508	Peto Odds Ratio (99% CI)	1.42 [0.82, 2.46]
25.4 60 years and older	9	174	Peto Odds Ratio (99% CI)	1.67 [0.65, 4.29]
26 SM free survival - non-malignant skin cancers excluded	16	2861	Peto Odds Ratio (99% CI)	1.32 [0.95, 1.84]
26.1 advanced stages	13	2165	Peto Odds Ratio (99% CI)	1.35 [0.95, 1.92]
26.2 early stages	4	696	Peto Odds Ratio (99% CI)	1.17 [0.48, 2.83]
27 SM before progression/relapse - non-malignant skin cancers excluded	16	2857	Peto Odds Ratio (99% CI)	1.53 [1.03, 2.26]
27.1 advanced stages	13	2165	Peto Odds Ratio (99% CI)	1.67 [1.09, 2.56]
27.2 early stages	4	692	Peto Odds Ratio (99% CI)	0.98 [0.37, 2.56]
28 solid tumors	15	2750	Peto Odds Ratio (99% CI)	1.29 [0.83, 2.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 advanced stages	12	2054	Peto Odds Ratio (99% CI)	1.36 [0.84, 2.20]
28.2 early stages	4	696	Peto Odds Ratio (99% CI)	0.97 [0.31, 3.02]
29 solid tumors - non-malignant skin cancers excluded	15	2750	Peto Odds Ratio (99% CI)	1.24 [0.78, 1.97]
29.1 advanced stages	12	2054	Peto Odds Ratio (99% CI)	1.31 [0.79, 2.16]
29.2 early stages	4	696	Peto Odds Ratio (99% CI)	0.97 [0.31, 3.02]
30 solid tumors before progression/relapse	15	2746	Peto Odds Ratio (99% CI)	1.60 [0.95, 2.68]
30.1 early stages	4	692	Peto Odds Ratio (99% CI)	1.07 [0.32, 3.52]
30.2 advanced stages	12	2054	Peto Odds Ratio (99% CI)	1.75 [0.99, 3.10]
31 lung cancers	12	2054	Peto Odds Ratio (99% CI)	1.59 [0.59, 4.27]
31.1 advanced stages	12	2054	Peto Odds Ratio (99% CI)	1.59 [0.59, 4.27]
32 breast cancers	12	739	Peto Odds Ratio (99% CI)	1.24 [0.25, 6.22]
32.1 advanced stages, female	12	739	Peto Odds Ratio (99% CI)	1.24 [0.25, 6.22]
33 AML/MDS	16	2861	Peto Odds Ratio (99% CI)	1.82 [0.95, 3.46]
33.1 advanced stages	13	2165	Peto Odds Ratio (99% CI)	1.70 [0.88, 3.29]
33.2 early stages	4	696	Peto Odds Ratio (99% CI)	6.03 [0.37, 99.07]
34 AML/MDS before progression/relapse	16	2861	Peto Odds Ratio (99% CI)	2.75 [1.25, 6.06]
34.1 advanced stages	13	2165	Peto Odds Ratio (99% CI)	2.57 [1.13, 5.85]
34.2 early stages	4	696	Peto Odds Ratio (99% CI)	6.03 [0.37, 99.07]
35 NHL	15	2750	Peto Odds Ratio (99% CI)	1.13 [0.51, 2.52]
35.1 advanced stages	12	2054	Peto Odds Ratio (99% CI)	1.19 [0.47, 3.00]
35.2 early stages	4	696	Peto Odds Ratio (99% CI)	0.97 [0.20, 4.82]
36 NHL before progression/relapse	12	2054	Peto Odds Ratio (99% CI)	1.23 [0.46, 3.29]
36.1 advanced stages	12	2054	Peto Odds Ratio (99% CI)	1.23 [0.46, 3.29]

Analysis 2.1. Comparison 2 CT v CRT, Outcome 1 overall survival.

Analysis 2.2. Comparison 2 CT v CRT, Outcome 2 OS - unconfounded trials.

Analysis 2.3. Comparison 2 CT v CRT, Outcome 3 OS - early stages - sex.

Study or subgroup	CT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Test for overall effect: $Z=2.69(P=0.01)$					
Test for subgroup differences: $\text{Chi}^2=0.71$, $\text{df}=1$ ($P=0.4$), $I^2=0\%$					
<div style="display: flex; justify-content: space-between;"> Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours CT </div>					

Analysis 2.4. Comparison 2 CT v CRT, Outcome 4 OS - advanced stages - sex.

Study or subgroup	CT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
2.4.3 male					
CALGB 6604	15/17	21/28		3.81%	0.59[0.21,1.63]
CALGB 7451	21/36	42/78		7.22%	0.89[0.43,1.87]
CALGB 7551	52/98	67/110		15.05%	1.16[0.7,1.94]
EORTC, #20884	11/102	18/110		4.12%	1.61[0.61,4.27]
GATLA 9-H-77	26/58	12/41		5.06%	0.55[0.23,1.32]
GELA H89	18/146	26/141		6.29%	1.59[0.72,3.49]
GHSG, HD3	11/32	12/37		2.94%	0.76[0.24,2.41]
Manchester, HD 2	11/21	9/27		2.69%	0.55[0.17,1.86]
NCI Canada, HD1	23/40	21/39		5.62%	0.91[0.39,2.1]
Obninsk, advanced	35/45	49/89		8.77%	0.48[0.25,0.93]
SJCRH, HD Study IIC	1/6	4/8		0.73%	3.19[0.32,32.28]
Stanf. C7-10, C12-15	8/26	6/21		2%	0.79[0.19,3.2]
Stanf. K7, S8	11/17	16/21		3.36%	1.08[0.37,3.18]
Subtotal (95% CI)	644	750		67.65%	0.9[0.75,1.08]
Total events: 243 (CT), 303 (CRT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=20.13$, $\text{df}=12$ ($P=0.06$); $I^2=40.37\%$					
Test for overall effect: $Z=1.18$ ($P=0.24$)					
2.4.4 female					
CALGB 6604	3/5	13/17		1.66%	1.51[0.32,7]
CALGB 7451	13/27	19/35		4.27%	1.31[0.5,3.4]
CALGB 7551	26/54	21/41		6.04%	1.11[0.5,2.48]
EORTC, #20884	5/59	10/62		2.14%	1.95[0.51,7.55]
GATLA 9-H-77	13/27	7/25		2.71%	0.47[0.14,1.55]
GELA H89	6/62	9/70		2.16%	1.33[0.35,5.13]
GHSG, HD3	1/17	4/14		0.71%	4.12[0.39,43.3]
Manchester, HD 2	2/10	4/7		0.79%	3.93[0.42,36.67]
NCI Canada, HD1	8/17	6/15		1.8%	0.91[0.21,4]
Obninsk, advanced	20/39	52/111		7.18%	0.83[0.4,1.74]
SJCRH, HD Study IIC	2/7	2/3		0.4%	4.42[0.19,100.38]
Stanf. C7-10, C12-15	6/14	5/13		1.36%	0.8[0.15,4.35]
Stanf. K7, S8	6/11	2/9		1.12%	0.4[0.06,2.58]
Subtotal (95% CI)	349	422		32.35%	1.07[0.82,1.4]
Total events: 111 (CT), 154 (CRT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=14.02$, $\text{df}=12$ ($P=0.3$); $I^2=14.38\%$					
Test for overall effect: $Z=0.52$ ($P=0.6$)					
Total (95% CI)	993	1172		100%	0.95[0.82,1.1]
Total events: 354 (CT), 457 (CRT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=35.35$, $\text{df}=25$ ($P=0.08$); $I^2=29.28\%$					
<div style="display: flex; justify-content: space-between;"> Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours CT </div>					

Study or subgroup	CT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Test for overall effect: $Z=0.68(P=0.5)$					
Test for subgroup differences: $\text{Chi}^2=1.21$, $\text{df}=1$ ($P=0.27$), $I^2=17.4\%$					
<div style="display: flex; justify-content: space-between;"> Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours CT </div>					

Analysis 2.5. Comparison 2 CT v CRT, Outcome 5 OS- early stages - age.

Study or subgroup	Treatment: CT n/N	Control: CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
2.5.1 0-15 years					
GATLA 9-H-77	7/80	5/51		8.75%	1.07[0.23,4.93]
Subtotal (95% CI)	80	51		8.75%	1.07[0.33,3.42]
Total events: 7 (Treatment: CT), 5 (Control: CRT)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.11(P=0.91)$					
2.5.2 16-39 years					
CALGB 7751	6/23	4/20		7.39%	0.76[0.14,4.03]
GATLA 9-H-77	11/45	14/62		17.97%	0.85[0.29,2.48]
Mexico, 82HO31	34/62	14/74		31.88%	0.26[0.11,0.57]
MSKCC, trial # 90-44	4/45	2/55		4.48%	0.36[0.04,3.06]
Subtotal (95% CI)	175	211		61.72%	0.42[0.27,0.66]
Total events: 55 (Treatment: CT), 34 (Control: CRT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=6.32$, $\text{df}=3$ ($P=0.1$); $I^2=52.55\%$					
Test for overall effect: $Z=3.84(P=0)$					
2.5.3 age 40+					
CALGB 7751	3/8	5/9		5.69%	1.82[0.27,12.14]
GATLA 9-H-77	8/28	7/30		10.95%	0.78[0.2,3.08]
Mexico, 82HO31	9/37	6/28		10.73%	0.84[0.21,3.35]
MSKCC, trial # 90-44	3/25	0/15		2.16%	0.19[0.01,4.14]
Subtotal (95% CI)	98	82		29.53%	0.85[0.45,1.61]
Total events: 23 (Treatment: CT), 18 (Control: CRT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=2.65$, $\text{df}=3$ ($P=0.45$); $I^2=0\%$					
Test for overall effect: $Z=0.49(P=0.62)$					
Total (95% CI)	353	344		100%	0.56[0.4,0.8]
Total events: 85 (Treatment: CT), 57 (Control: CRT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=13.38$, $\text{df}=8$ ($P=0.1$); $I^2=40.23\%$					
Test for overall effect: $Z=3.25(P=0)$					
Test for subgroup differences: $\text{Chi}^2=4.41$, $\text{df}=1$ ($P=0.11$), $I^2=54.67\%$					
<div style="display: flex; justify-content: space-between;"> Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours CT </div>					

Analysis 2.6. Comparison 2 CT v CRT, Outcome 6 OS - advanced stages - age.

Study or subgroup	CT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
2.6.1 0-15 years					
<div style="display: flex; justify-content: space-between;"> Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours CT </div>

Analysis 2.7. Comparison 2 CT v CRT, Outcome 7 OS - early stages - type of RT.

Analysis 2.8. Comparison 2 CT v CRT, Outcome 8 OS - advanced stages - type of RT.

Analysis 2.9. Comparison 2 CT v CRT, Outcome 9 PFS confounded advanced.

Analysis 2.10. Comparison 2 CT v CRT, Outcome 10 progression free survival.

Analysis 2.11. Comparison 2 CT v CRT, Outcome 11 PFS - censored at cut-off date.

Analysis 2.12. Comparison 2 CT v CRT, Outcome 12 PFS - unconfounded trials only.

Analysis 2.13. Comparison 2 CT v CRT, Outcome 13 PFS - early stages - sex.

Analysis 2.14. Comparison 2 CT v CRT, Outcome 14 PFS - advanced stages - sex.

Study or subgroup	CT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Heterogeneity: $\tau^2=0$; $\chi^2=34.42$, $df=25$ ($P=0.1$); $I^2=27.36\%$ Test for overall effect: $Z=2.7$ ($P=0.01$) Test for subgroup differences: $\chi^2=0.02$, $df=1$ ($P=0.89$), $I^2=0\%$					
			Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours CT		

Analysis 2.15. Comparison 2 CT v CRT, Outcome 15 PFS - early stages - age.

Study or subgroup	CT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
2.15.1 0-15 years					
GATLA 9-H-77	26/80	16/50		17.45%	0.88[0.38,2.05]
Subtotal (95% CI)	80	50		17.45%	0.88[0.46,1.68]
Total events: 26 (CT), 16 (CRT) Heterogeneity: Not applicable Test for overall effect: $Z=0.38$ ($P=0.7$)					
2.15.2 16-39 years					
CALGB 7751	13/23	5/20		7.47%	0.32[0.09,1.15]
GATLA 9-H-77	25/45	20/62		17.47%	0.42[0.18,0.97]
Mexico, 82HO31	40/62	27/74		24.29%	0.39[0.19,0.79]
MSKCC, trial # 90-44	10/45	8/54		7.7%	0.6[0.17,2.13]
Subtotal (95% CI)	175	210		56.92%	0.41[0.29,0.58]
Total events: 88 (CT), 60 (CRT) Heterogeneity: $\tau^2=0$; $\chi^2=0.9$, $df=3$ ($P=0.82$); $I^2=0\%$ Test for overall effect: $Z=4.92$ ($P<0.0001$)					
2.15.3 age 40+					
CALGB 7751	4/8	5/9		3.47%	1.38[0.21,9.13]
GATLA 9-H-77	13/28	11/27		9.9%	0.67[0.22,2.04]
Mexico, 82HO31	15/37	9/28		10.11%	0.73[0.24,2.22]
MSKCC, trial # 90-44	3/24	2/14		2.15%	1.04[0.09,11.44]
Subtotal (95% CI)	97	78		25.63%	0.79[0.47,1.35]
Total events: 35 (CT), 27 (CRT) Heterogeneity: $\tau^2=0$; $\chi^2=0.84$, $df=3$ ($P=0.84$); $I^2=0\%$ Test for overall effect: $Z=0.86$ ($P=0.39$)					
Total (95% CI)	352	338		100%	0.56[0.42,0.73]
Total events: 149 (CT), 103 (CRT) Heterogeneity: $\tau^2=0$; $\chi^2=8.3$, $df=8$ ($P=0.41$); $I^2=3.57\%$ Test for overall effect: $Z=4.31$ ($P<0.0001$) Test for subgroup differences: $\chi^2=6.55$, $df=1$ ($P=0.04$), $I^2=69.48\%$					
			Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours CT		

Analysis 2.16. Comparison 2 CT v CRT, Outcome 16 PFS - advanced stages - age.

Analysis 2.17. Comparison 2 CT v CRT, Outcome 17 second malignancy free survival.

Analysis 2.18. Comparison 2 CT v CRT, Outcome 18 SM free survival - censored at cut-off date.

Analysis 2.19. Comparison 2 CT v CRT, Outcome 19 SM free survival - unconfounded trials only.

Analysis 2.20. Comparison 2 CT v CRT, Outcome 20 SM free survival - confounded trials only.

Analysis 2.21. Comparison 2 CT v CRT, Outcome 21 SM before progression or relapse.

Analysis 2.22. Comparison 2 CT v CRT, Outcome 22 SM free survival - early stages - sex.

Analysis 2.23. Comparison 2 CT v CRT, Outcome 23 SM free survival - advanced stages - sex.

Analysis 2.24. Comparison 2 CT v CRT, Outcome 24 SM free survival - early stages - age.

Analysis 2.25. Comparison 2 CT v CRT, Outcome 25 SM free survival - advanced stages - age.

Analysis 2.26. Comparison 2 CT v CRT, Outcome 26 SM free survival - non-malignant skin cancers excluded.

Analysis 2.27. Comparison 2 CT v CRT, Outcome 27 SM before progression/relapse - non-malignant skin cancers excluded.

Analysis 2.28. Comparison 2 CT v CRT, Outcome 28 solid tumors.

Analysis 2.29. Comparison 2 CT v CRT, Outcome 29 solid tumors - non-malignant skin cancers excluded.

Analysis 2.30. Comparison 2 CT v CRT, Outcome 30 solid tumors before progression/relapse.

Analysis 2.31. Comparison 2 CT v CRT, Outcome 31 lung cancers.

Analysis 2.32. Comparison 2 CT v CRT, Outcome 32 breast cancers.

Study or subgroup	CT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Heterogeneity: $\tau^2=0$; $\chi^2=6.51$, $df=4$ ($P=0.16$); $I^2=38.58\%$ Test for overall effect: $Z=0.26$ ($P=0.79$)

Analysis 2.33. Comparison 2 CT v CRT, Outcome 33 AML/MDS.

Study or subgroup	CT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
2.33.1 advanced stages					
CALGB 6604	0/22	0/45			Not estimable
CALGB 7451	0/63	0/113			Not estimable
CALGB 7551	1/152	1/151		5.18%	1.34[0.03,55.12]
EORTC, #20884	1/161	8/172		23.87%	4.62[0.82,26.1]
GATLA 9-H-77	0/85	0/66			Not estimable
GELA H89	2/208	2/211		10.8%	1.01[0.08,13.27]
GHSG, HD3	0/49	2/51		5.29%	6.54[0.16,259.12]
Manchester, HD 2	1/31	3/34		10.48%	2.5[0.18,34.22]
NCI Canada, HD1	2/57	2/54		10.48%	1.05[0.08,14.4]
Obninsk, advanced	0/84	1/200		2.27%	4.17[0.02,1152.27]
SJCRH, HD Study IIC	0/13	0/11			Not estimable
Stanf. C7-10, C12-15	3/40	2/34		13.28%	0.7[0.07,7.19]
Stanf. K7, S8	3/28	2/30		13.07%	0.6[0.06,6.23]
Subtotal (95% CI)	993	1172		94.71%	1.7[0.88,3.29]
Total events: 13 (CT), 23 (CRT) Heterogeneity: $\tau^2=0$; $\chi^2=6.2$, $df=8$ ($P=0.63$); $I^2=0\%$ Test for overall effect: $Z=1.57$ ($P=0.12$)					
2.33.2 early stages					
CALGB 7751	0/32	0/29			Not estimable
GATLA 9-H-77	0/153	0/140			Not estimable
Mexico, 82HO31	0/99	2/102		5.29%	6.03[0.15,238.81]
MSKCC, trial # 90-44	0/70	0/71			Not estimable
Subtotal (95% CI)	354	342		5.29%	6.03[0.37,99.07]
Total events: 0 (CT), 2 (CRT) Heterogeneity: Not applicable Test for overall effect: $Z=1.26$ ($P=0.21$)					
Total (95% CI)	1347	1514		100%	1.82[0.95,3.46]
Total events: 13 (CT), 25 (CRT) Heterogeneity: $\tau^2=0$; $\chi^2=6.94$, $df=9$ ($P=0.64$); $I^2=0\%$ Test for overall effect: $Z=1.81$ ($P=0.07$) Test for subgroup differences: $\chi^2=0.74$, $df=1$ ($P=0.39$), $I^2=0\%$					

Analysis 2.34. Comparison 2 CT v CRT, Outcome 34 AML/MDS before progression/relapse.

Analysis 2.35. Comparison 2 CT v CRT, Outcome 35 NHL.

Analysis 2.36. Comparison 2 CT v CRT, Outcome 36 NHL before progression/relapse.

Comparison 3. RT v CRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 overall survival	15	3343	Peto Odds Ratio (99% CI)	0.76 [0.66, 0.89]
1.1 early stages	13	3054	Peto Odds Ratio (99% CI)	0.71 [0.60, 0.85]
1.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.97 [0.70, 1.34]
2 OS - early stages - sex	13	3054	Peto Odds Ratio (99% CI)	0.72 [0.60, 0.85]
2.1 female	13	1262	Peto Odds Ratio (99% CI)	0.82 [0.62, 1.10]
2.2 male	13	1792	Peto Odds Ratio (99% CI)	0.67 [0.54, 0.82]
3 OS - advanced stages - sex	3	288	Peto Odds Ratio (99% CI)	1.04 [0.75, 1.44]
3.1 female	3	98	Peto Odds Ratio (99% CI)	1.21 [0.67, 2.19]
3.2 male	3	190	Peto Odds Ratio (99% CI)	0.97 [0.65, 1.44]
4 OS - early stages - age	13	3039	Peto Odds Ratio (99% CI)	0.75 [0.63, 0.89]
4.1 0-15 years	6	70	Peto Odds Ratio (99% CI)	1.45 [0.50, 4.21]
4.2 16-39 years	13	2132	Peto Odds Ratio (99% CI)	0.67 [0.53, 0.84]
4.3 40-59 years	12	720	Peto Odds Ratio (99% CI)	0.80 [0.58, 1.09]
4.4 60+ years	6	117	Peto Odds Ratio (99% CI)	1.05 [0.57, 1.93]
5 OS - advanced stages - age	3	277	Peto Odds Ratio (99% CI)	1.08 [0.78, 1.51]
5.2 16-39 years	3	188	Peto Odds Ratio (99% CI)	0.95 [0.61, 1.46]
5.3 40+ years	3	89	Peto Odds Ratio (99% CI)	1.30 [0.78, 2.19]
6 OS - unconfounded trials only	9	1674	Peto Odds Ratio (99% CI)	0.78 [0.64, 0.95]
6.1 early stages	7	1385	Peto Odds Ratio (99% CI)	0.69 [0.54, 0.89]
6.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.97 [0.70, 1.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 progression free survival	15	3343	Peto Odds Ratio (99% CI)	0.49 [0.43, 0.56]
7.1 early stages	13	3054	Peto Odds Ratio (99% CI)	0.46 [0.40, 0.53]
7.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.72 [0.52, 1.00]
8 PFS - early stages - sex	13	3054	Peto Odds Ratio (99% CI)	0.45 [0.39, 0.52]
8.1 female	13	1262	Peto Odds Ratio (99% CI)	0.51 [0.41, 0.65]
8.2 male	13	1792	Peto Odds Ratio (99% CI)	0.42 [0.35, 0.50]
9 PFS - advanced stages - sex	3	288	Peto Odds Ratio (99% CI)	0.76 [0.54, 1.05]
9.1 female	3	98	Peto Odds Ratio (99% CI)	0.74 [0.42, 1.31]
9.2 male	3	190	Peto Odds Ratio (99% CI)	0.76 [0.51, 1.15]
10 PFS - early stages - age	13	3039	Peto Odds Ratio (99% CI)	0.46 [0.40, 0.53]
10.1 0-15 years	6	70	Peto Odds Ratio (99% CI)	0.69 [0.30, 1.62]
10.2 16-39 years	13	2132	Peto Odds Ratio (99% CI)	0.42 [0.35, 0.50]
10.3 40-59 years	12	720	Peto Odds Ratio (99% CI)	0.48 [0.36, 0.63]
10.4 60+ years	6	117	Peto Odds Ratio (99% CI)	0.97 [0.53, 1.77]
11 PFS - advanced stages - age	3	277	Peto Odds Ratio (99% CI)	0.77 [0.54, 1.08]
11.1 16-39 years	3	188	Peto Odds Ratio (99% CI)	0.62 [0.40, 0.95]
11.2 40+ years	3	89	Peto Odds Ratio (99% CI)	1.10 [0.63, 1.94]
12 PFS - censored at cut-off date	15	3343	Peto Odds Ratio (99% CI)	0.48 [0.42, 0.55]
12.1 early stages	13	3054	Peto Odds Ratio (99% CI)	0.44 [0.38, 0.51]
12.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.79 [0.57, 1.11]
13 PFS - unconfounded trials only	9	1674	Peto Odds Ratio (99% CI)	0.51 [0.43, 0.60]
13.1 early stages	7	1385	Peto Odds Ratio (99% CI)	0.45 [0.37, 0.55]
13.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.72 [0.52, 1.00]
14 second malignancy free survival	15	3342	Peto Odds Ratio (99% CI)	0.79 [0.63, 0.98]
14.1 early stages	13	3053	Peto Odds Ratio (99% CI)	0.84 [0.66, 1.06]
14.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.45 [0.23, 0.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 SM free survival - censored at cutt-off date	15	3342	Peto Odds Ratio (99% CI)	0.86 [0.67, 1.11]
15.1 early stages	13	3053	Peto Odds Ratio (99% CI)	0.93 [0.72, 1.21]
15.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.43 [0.20, 0.94]
16 SM free survival - unconfounded trials only	9	1673	Peto Odds Ratio (99% CI)	0.82 [0.60, 1.12]
16.1 early stages	7	1384	Peto Odds Ratio (99% CI)	0.95 [0.67, 1.35]
16.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.45 [0.23, 0.90]
17 SM free survival - confounded trials only	6	1669	Peto Odds Ratio (99% CI)	0.75 [0.54, 1.03]
17.1 early stages	6	1669	Peto Odds Ratio (99% CI)	0.75 [0.54, 1.03]
18 SM before progression/relapse	15	3343	Peto Odds Ratio (99% CI)	1.11 [0.82, 1.48]
18.1 early stages	13	3054	Peto Odds Ratio (99% CI)	1.14 [0.84, 1.56]
18.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.76 [0.27, 2.11]
19 SM free survival - early stages - sex	13	3053	Peto Odds Ratio (99% CI)	0.83 [0.65, 1.05]
19.1 female	13	1261	Peto Odds Ratio (99% CI)	0.92 [0.65, 1.32]
19.2 male	13	1792	Peto Odds Ratio (99% CI)	0.76 [0.55, 1.05]
20 SM free survival - advanced stages - sex	3	288	Peto Odds Ratio (99% CI)	0.47 [0.23, 0.96]
20.1 female	3	98	Peto Odds Ratio (99% CI)	0.36 [0.11, 1.13]
20.2 male	3	190	Peto Odds Ratio (99% CI)	0.56 [0.23, 1.38]
21 SM free survival - early stages - age	13	3038	Peto Odds Ratio (99% CI)	0.86 [0.67, 1.09]
21.1 0-15 years	6	70	Peto Odds Ratio (99% CI)	1.12 [0.41, 3.03]
21.2 16-39 years	13	2131	Peto Odds Ratio (99% CI)	0.70 [0.51, 0.97]
21.3 40-59 years	12	720	Peto Odds Ratio (99% CI)	1.07 [0.69, 1.67]
21.4 60+ years	6	117	Peto Odds Ratio (99% CI)	1.26 [0.50, 3.20]
22 SM free survival - advanced stages - age	3	277	Peto Odds Ratio (99% CI)	0.40 [0.19, 0.82]
22.1 16-39 years	3	188	Peto Odds Ratio (99% CI)	0.41 [0.16, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 40+ years	3	89	Peto Odds Ratio (99% CI)	0.37 [0.12, 1.20]
23 SM free survival - subgroup +/- mustargen	13	3053	Peto Odds Ratio (99% CI)	0.84 [0.66, 1.06]
23.1 without mustargen	7	1522	Peto Odds Ratio (99% CI)	0.85 [0.54, 1.34]
23.2 with mustargen	6	1531	Peto Odds Ratio (99% CI)	0.83 [0.63, 1.10]
24 SM free survival - non-malignant skin cancers excluded	15	3342	Peto Odds Ratio (99% CI)	0.81 [0.64, 1.03]
24.1 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.46 [0.22, 0.96]
24.2 early stages	13	3053	Peto Odds Ratio (99% CI)	0.87 [0.68, 1.12]
25 SM before progression/relapse - non-malignant skin cancers excluded	15	3342	Peto Odds Ratio (99% CI)	1.10 [0.81, 1.49]
25.1 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.76 [0.25, 2.29]
25.2 early stages	13	3053	Peto Odds Ratio (99% CI)	1.13 [0.82, 1.56]
26 solid tumors	15	3343	Peto Odds Ratio (99% CI)	0.78 [0.60, 1.00]
26.1 early stages	13	3054	Peto Odds Ratio (99% CI)	0.83 [0.63, 1.09]
26.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.44 [0.20, 0.97]
27 solid tumors - non-malignant skin cancers excluded	15	3343	Peto Odds Ratio (99% CI)	0.82 [0.62, 1.08]
27.1 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.44 [0.18, 1.05]
27.2 early stages	13	3054	Peto Odds Ratio (99% CI)	0.88 [0.65, 1.17]
28 solid tumors before progression/relapse	15	3343	Peto Odds Ratio (99% CI)	1.07 [0.77, 1.51]
28.1 early stages	13	3054	Peto Odds Ratio (99% CI)	1.09 [0.77, 1.56]
28.2 advanced stages	3	289	Peto Odds Ratio (99% CI)	0.89 [0.28, 2.84]
29 lung cancers	13	3054	Peto Odds Ratio (99% CI)	1.05 [0.58, 1.89]
29.1 early stages	13	3054	Peto Odds Ratio (99% CI)	1.05 [0.58, 1.89]
30 lung cancers before prog/rel	13	3054	Peto Odds Ratio (99% CI)	1.84 [0.87, 3.89]
30.1 early stages	13	3054	Peto Odds Ratio (99% CI)	1.84 [0.87, 3.89]
31 breast cancers	13	1262	Peto Odds Ratio (99% CI)	0.98 [0.50, 1.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 early stages	13	1262	Peto Odds Ratio (99% CI)	0.98 [0.50, 1.91]
32 AML/MDS - early stages only	13	3054	Peto Odds Ratio (99% CI)	1.55 [0.78, 3.07]
33 AML/MDS before progression/relapse	14	3056	Peto Odds Ratio (99% CI)	3.40 [1.31, 8.82]
33.1 early stages	14	3056	Peto Odds Ratio (99% CI)	3.40 [1.31, 8.82]
34 NHL - early stages only	13	3054	Peto Odds Ratio (99% CI)	0.46 [0.22, 0.94]
35 NHL before progression/relapse	13	3054	Peto Odds Ratio (99% CI)	0.68 [0.29, 1.62]
35.1 early stages	13	3054	Peto Odds Ratio (99% CI)	0.68 [0.29, 1.62]

Analysis 3.1. Comparison 3 RT v CRT, Outcome 1 overall survival.

Study or subgroup	RT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Heterogeneity: $\tau^2=0$; $\chi^2=34.36$, $df=15$ ($P=0$); $I^2=56.35\%$					
Test for overall effect: $Z=3.52$ ($P=0$)					
Test for subgroup differences: $\chi^2=2.77$, $df=1$ ($P=0.1$), $I^2=63.95\%$					
			Favours CRT		Favours RT

Analysis 3.2. Comparison 3 RT v CRT, Outcome 2 OS - early stages - sex.

Study or subgroup	RT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
3.2.1 female					
Manchester, RT v. CRT	2/22	4/30		1.05%	1.37[0.15,12.23]
EORTC, H5U	13/52	11/45		4.29%	0.96[0.33,2.84]
EORTC, H7F	3/70	3/70		1.13%	0.93[0.11,7.66]
EORTC-GELA, H8F	3/108	1/96		0.75%	0.43[0.03,5.76]
GHSG, HD7	4/130	6/123		1.89%	1.55[0.3,7.93]
Lygra II	23/63	18/67		7.41%	0.72[0.32,1.65]
Manchester, HD 1	7/17	9/20		2.75%	1.09[0.28,4.2]
Mexico, 82HO31	28/56	11/51		6.69%	0.38[0.16,0.91]
Rome, RT vs. CRT	1/29	2/35		0.56%	1.76[0.09,35.23]
SJCRH, HD study II B	4/10	1/7		0.91%	0.36[0.03,3.74]
Stanf. C1-C3, G1	2/21	1/22		0.56%	0.43[0.02,8.64]
Stanf. S1	3/23	6/19		1.63%	2.77[0.48,16.04]
Stanf. H2-H6, K1, R1	14/35	17/41		5.23%	1.2[0.45,3.2]
Subtotal (95% CI)	636	626		34.84%	0.82[0.62,1.1]
Total events: 107 (RT), 90 (CRT)					
Heterogeneity: $\tau^2=0$; $\chi^2=13.3$, $df=12$ ($P=0.35$); $I^2=9.76\%$					
Test for overall effect: $Z=1.33$ ($P=0.18$)					
3.2.2 male					
EORTC, H5U	38/100	33/99		12.38%	0.86[0.46,1.64]
EORTC, H7F	8/94	7/98		2.75%	0.85[0.22,3.29]
EORTC-GELA, H8F	14/162	1/172		2.81%	0.15[0.04,0.59]
GHSG, HD7	15/181	13/192		5.23%	0.8[0.3,2.13]
Lygra II	52/101	40/95		15.86%	0.78[0.44,1.37]
Manchester, HD 1	17/39	14/39		5.32%	0.72[0.27,1.9]
Manchester, RT v. CRT	11/40	8/32		3.28%	0.89[0.26,3.07]
Mexico, 82HO31	23/50	9/51		5.37%	0.31[0.12,0.81]
Rome, RT vs. CRT	0/19	1/19		0.19%	7.39[0.04,1276.22]
SJCRH, HD study II B	0/3	1/4		0.18%	6[0.03,1152.35]
Stanf. C1-C3, G1	4/36	0/27		0.74%	0.16[0.01,2.13]
Stanf. S1	8/12	5/17		2.18%	0.35[0.08,1.59]
Stanf. H2-H6, K1, R1	33/63	20/47		8.85%	0.76[0.36,1.62]
Subtotal (95% CI)	900	892		65.16%	0.67[0.54,0.82]
Total events: 223 (RT), 152 (CRT)					
Heterogeneity: $\tau^2=0$; $\chi^2=20.61$, $df=12$ ($P=0.06$); $I^2=41.76\%$					
Test for overall effect: $Z=3.77$ ($P=0$)					
Total (95% CI)	1536	1518		100%	0.72[0.6,0.85]
Total events: 330 (RT), 242 (CRT)					
			Favours CRT		Favours RT

Analysis 3.3. Comparison 3 RT v CRT, Outcome 3 OS - advanced stages - sex.

Analysis 3.4. Comparison 3 RT v CRT, Outcome 4 OS - early stages - age.

Analysis 3.5. Comparison 3 RT v CRT, Outcome 5 OS - advanced stages - age.

Analysis 3.6. Comparison 3 RT v CRT, Outcome 6 OS - unconfounded trials only.

Analysis 3.7. Comparison 3 RT v CRT, Outcome 7 progression free survival.

Analysis 3.8. Comparison 3 RT v CRT, Outcome 8 PFS - early stages - sex.

Analysis 3.9. Comparison 3 RT v CRT, Outcome 9 PFS - advanced stages - sex.

Analysis 3.10. Comparison 3 RT v CRT, Outcome 10 PFS - early stages - age.

Analysis 3.11. Comparison 3 RT v CRT, Outcome 11 PFS - advanced stages - age.

Analysis 3.12. Comparison 3 RT v CRT, Outcome 12 PFS - censored at cut-off date.

Analysis 3.13. Comparison 3 RT v CRT, Outcome 13 PFS - unconfounded trials only.

Analysis 3.14. Comparison 3 RT v CRT, Outcome 14 second malignancy free survival.

Analysis 3.15. Comparison 3 RT v CRT, Outcome 15 SM free survival - censored at cutt-off date.

Analysis 3.16. Comparison 3 RT v CRT, Outcome 16 SM free survival - unconfounded trials only.

Analysis 3.17. Comparison 3 RT v CRT, Outcome 17 SM free survival - confounded trials only.

Study or subgroup	RT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Heterogeneity: $\tau^2=0$; $\chi^2=10.21$, $df=5$ ($P=0.07$); $I^2=51.04\%$ Test for overall effect: $Z=1.75$ ($P=0.08$)					
Favours CRT 0.01 0.1 1 10 100 Favours RT					

Analysis 3.18. Comparison 3 RT v CRT, Outcome 18 SM before progression/relapse.

Study or subgroup	RT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
3.18.1 early stages					
EORTC, HSU	10/152	18/144		15.05%	1.64[0.61,4.45]
EORTC, H7F	6/164	1/168		3.9%	0.21[0.03,1.49]
EORTC-GELA, H8F	4/270	3/268		3.88%	0.65[0.09,4.61]
GHSG, HD7	14/311	14/315		15.26%	0.95[0.35,2.55]
Lygra II	0/164	2/162		1.13%	7.54[0.2,287.95]
Manchester, HD 1	6/56	3/59		4.78%	0.36[0.06,2.1]
Manchester, RT v. CRT	3/62	6/62		4.85%	1.68[0.29,9.71]
Mexico, 82HO31	0/106	3/102		1.65%	5.85[0.29,119.33]
Rome, RT vs. CRT	1/48	4/54		2.64%	3.45[0.32,37.36]
SJCRH, HD study II B	2/13	5/11		3.32%	1.71[0.2,14.32]
Stanf. C1-C3, G1	4/57	2/49		3.29%	0.47[0.06,3.94]
Stanf. S1	7/35	11/36		9.39%	1.64[0.47,5.82]
Stanf. H2-H6, K1, R1	20/98	23/88		22.5%	1.16[0.52,2.63]
Subtotal (95% CI)	1536	1518		91.65%	1.14[0.84,1.56]
Total events: 77 (RT), 95 (CRT) Heterogeneity: $\tau^2=0$; $\chi^2=16.94$, $df=12$ ($P=0.15$); $I^2=29.15\%$ Test for overall effect: $Z=0.85$ ($P=0.39$)					
3.18.2 advanced stages					
CALGB 6604	0/18	1/22		0.56%	6.05[0.04,1044.88]
CALGB 7451	2/53	0/113		0.93%	0.03[0,1.79]
Stanf. H2-H6, K1, R1	5/43	11/40		6.86%	0.98[0.22,4.31]
Subtotal (95% CI)	114	175		8.35%	0.76[0.27,2.11]
Total events: 7 (RT), 12 (CRT) Heterogeneity: $\tau^2=0$; $\chi^2=5.38$, $df=2$ ($P=0.07$); $I^2=62.85\%$ Test for overall effect: $Z=0.53$ ($P=0.6$)					
Total (95% CI)	1650	1693		100%	1.11[0.82,1.48]
Total events: 84 (RT), 107 (CRT) Heterogeneity: $\tau^2=0$; $\chi^2=22.88$, $df=15$ ($P=0.09$); $I^2=34.45\%$ Test for overall effect: $Z=0.67$ ($P=0.51$) Test for subgroup differences: $\chi^2=0.56$, $df=1$ ($P=0.45$), $I^2=0\%$					
Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours RT					

Analysis 3.19. Comparison 3 RT v CRT, Outcome 19 SM free survival - early stages - sex.

Analysis 3.20. Comparison 3 RT v CRT, Outcome 20 SM free survival - advanced stages - sex.

Analysis 3.21. Comparison 3 RT v CRT, Outcome 21 SM free survival - early stages - age.

Analysis 3.22. Comparison 3 RT v CRT, Outcome 22 SM free survival - advanced stages - age.

Analysis 3.23. Comparison 3 RT v CRT, Outcome 23 SM free survival - subgroup +/- mustargen.

Analysis 3.24. Comparison 3 RT v CRT, Outcome 24 SM free survival - non-malignant skin cancers excluded.

Study or subgroup	RT n/N	CRT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Test for subgroup differences: $\chi^2=2.56$, $df=1$ ($P=0.11$), $I^2=61.01\%$					
			Favours CRT 0.1 0.2 0.5 1 2 5 10 Favours RT		

Analysis 3.25. Comparison 3 RT v CRT, Outcome 25 SM before progression/relapse - non-malignant skin cancers excluded.

Analysis 3.26. Comparison 3 RT v CRT, Outcome 26 solid tumors.

Analysis 3.27. Comparison 3 RT v CRT, Outcome 27 solid tumors - non-malignant skin cancers excluded.

Analysis 3.28. Comparison 3 RT v CRT, Outcome 28 solid tumors before progression/relapse.

Analysis 3.29. Comparison 3 RT v CRT, Outcome 29 lung cancers.

Analysis 3.30. Comparison 3 RT v CRT, Outcome 30 lung cancers before prog/rel.

Analysis 3.31. Comparison 3 RT v CRT, Outcome 31 breast cancers.

Analysis 3.32. Comparison 3 RT v CRT, Outcome 32 AML/MDS - early stages only.

Analysis 3.33. Comparison 3 RT v CRT, Outcome 33 AML/MDS before progression/relapse.

Analysis 3.34. Comparison 3 RT v CRT, Outcome 34 NHL - early stages only.

Analysis 3.35. Comparison 3 RT v CRT, Outcome 35 NHL before progression/relapse.

Comparison 4. IF-RT vs. EF-RT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 overall survival	10	3221	Peto Odds Ratio (99% CI)	0.91 [0.77, 1.08]
1.1 advanced stages	3	295	Peto Odds Ratio (99% CI)	0.66 [0.48, 0.92]
1.2 early stages	8	2926	Peto Odds Ratio (99% CI)	1.03 [0.84, 1.26]
2 OS - RT plus CT	8	2962	Peto Odds Ratio (99% CI)	0.90 [0.73, 1.10]
2.1 early stages	6	2717	Peto Odds Ratio (99% CI)	1.06 [0.83, 1.35]
2.2 advanced stages	2	245	Peto Odds Ratio (99% CI)	0.61 [0.42, 0.88]
3 OS - RT without CT	2	259	Peto Odds Ratio (99% CI)	0.95 [0.69, 1.32]
3.1 early stages	2	209	Peto Odds Ratio (99% CI)	0.96 [0.67, 1.37]
3.2 advanced stages	1	50	Peto Odds Ratio (99% CI)	0.93 [0.44, 1.96]
4 OS - early stages - sex	8	2926	Peto Odds Ratio (99% CI)	1.03 [0.84, 1.26]
4.1 female patients	8	1531	Peto Odds Ratio (99% CI)	0.98 [0.70, 1.37]
4.2 male patients	8	1395	Peto Odds Ratio (99% CI)	1.06 [0.83, 1.37]
5 OS - advanced stages - sex	3	295	Peto Odds Ratio (99% CI)	0.68 [0.49, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 female patients	3	149	Peto Odds Ratio (99% CI)	0.56 [0.35, 0.91]
5.2 male patients	3	146	Peto Odds Ratio (99% CI)	0.80 [0.52, 1.25]
6 OS - early stages - age	8	2921	Peto Odds Ratio (99% CI)	1.05 [0.85, 1.29]
6.1 0-15 years	4	55	Peto Odds Ratio (99% CI)	1.59 [0.62, 4.05]
6.2 16-39 years	8	2042	Peto Odds Ratio (99% CI)	0.95 [0.72, 1.24]
6.3 40-59 years	8	631	Peto Odds Ratio (99% CI)	0.90 [0.58, 1.38]
6.4 60+ years	6	193	Peto Odds Ratio (99% CI)	1.73 [1.01, 2.96]
7 OS - advanced stages - age	3	277	Peto Odds Ratio (99% CI)	0.70 [0.50, 0.98]
7.1 16-39 years	3	210	Peto Odds Ratio (99% CI)	0.76 [0.51, 1.15]
7.2 40+ years	3	67	Peto Odds Ratio (99% CI)	0.56 [0.30, 1.05]
8 progression free survival	10	3215	Peto Odds Ratio (99% CI)	0.82 [0.70, 0.97]
8.1 early stages	8	2920	Peto Odds Ratio (99% CI)	0.90 [0.75, 1.08]
8.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	0.61 [0.44, 0.85]
9 PFS - censored at cut-off date	10	3215	Peto Odds Ratio (99% CI)	0.82 [0.69, 0.97]
9.1 early stages	8	2920	Peto Odds Ratio (99% CI)	0.90 [0.74, 1.08]
9.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	0.62 [0.44, 0.87]
10 PFS - RT plus CT	8	2956	Peto Odds Ratio (99% CI)	0.86 [0.72, 1.04]
10.1 early stages	6	2711	Peto Odds Ratio (99% CI)	0.98 [0.79, 1.22]
10.2 advanced stages	2	245	Peto Odds Ratio (99% CI)	0.60 [0.42, 0.86]
11 PFS - RT without CT	2	259	Peto Odds Ratio (99% CI)	0.72 [0.52, 0.99]
11.1 early stages	2	209	Peto Odds Ratio (99% CI)	0.72 [0.51, 1.02]
11.2 advanced stages	1	50	Peto Odds Ratio (99% CI)	0.69 [0.31, 1.56]
12 PFS - early stages - sex	8	2920	Peto Odds Ratio (99% CI)	0.90 [0.75, 1.09]
12.1 female patients	8	1528	Peto Odds Ratio (99% CI)	0.84 [0.62, 1.12]
12.2 male patients	8	1392	Peto Odds Ratio (99% CI)	0.95 [0.75, 1.20]
13 PFS - advanced stages - sex	3	295	Peto Odds Ratio (99% CI)	0.81 [0.58, 1.13]
13.1 female patients	3	149	Peto Odds Ratio (99% CI)	0.78 [0.48, 1.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 male patients	3	146	Peto Odds Ratio (99% CI)	0.83 [0.53, 1.32]
14 PFS - early stages - age	8	2915	Peto Odds Ratio (99% CI)	0.92 [0.76, 1.10]
14.1 0-15 years	4	55	Peto Odds Ratio (99% CI)	0.76 [0.31, 1.86]
14.2 16-39 years	8	2038	Peto Odds Ratio (99% CI)	0.86 [0.68, 1.10]
14.3 40-59 years	8	629	Peto Odds Ratio (99% CI)	0.80 [0.54, 1.19]
14.4 60+ years	6	193	Peto Odds Ratio (99% CI)	1.70 [0.99, 2.89]
15 PFS - advanced stages - age	3	277	Peto Odds Ratio (99% CI)	0.66 [0.47, 0.93]
15.1 16-39 years	3	210	Peto Odds Ratio (99% CI)	0.74 [0.50, 1.09]
15.2 40+ years	3	67	Peto Odds Ratio (99% CI)	0.48 [0.24, 0.95]
16 second malignancy free survival	10	3221	Peto Odds Ratio (99% CI)	1.17 [0.88, 1.57]
16.1 early stages	8	2926	Peto Odds Ratio (99% CI)	1.20 [0.88, 1.62]
16.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	0.95 [0.35, 2.61]
17 SM free survival - censored at cut-off date	10	3221	Peto Odds Ratio (99% CI)	1.13 [0.81, 1.57]
17.1 early stages	8	2926	Peto Odds Ratio (99% CI)	1.14 [0.81, 1.60]
17.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	0.94 [0.23, 3.88]
18 SM free survival - RT plus CT	8	2962	Peto Odds Ratio (99% CI)	1.33 [0.93, 1.90]
18.1 early stages	6	2717	Peto Odds Ratio (99% CI)	1.36 [0.94, 1.98]
18.2 advanced stages	2	245	Peto Odds Ratio (99% CI)	1.03 [0.30, 3.51]
19 SM free survival - RT without CT	2	259	Peto Odds Ratio (99% CI)	0.90 [0.54, 1.51]
19.1 early stages	2	209	Peto Odds Ratio (99% CI)	0.91 [0.54, 1.56]
19.2 advanced stages	1	50	Peto Odds Ratio (99% CI)	0.79 [0.13, 4.74]
20 SM before progression or relapse	10	3215	Peto Odds Ratio (99% CI)	1.54 [0.94, 2.52]
20.1 early stages	8	2920	Peto Odds Ratio (99% CI)	1.52 [0.91, 2.54]
20.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	1.77 [0.24, 13.11]
21 SM free survival - early stages - sex	8	2926	Peto Odds Ratio (99% CI)	1.17 [0.86, 1.58]
21.1 female patients	8	1531	Peto Odds Ratio (99% CI)	1.05 [0.66, 1.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.2 male patients	8	1395	Peto Odds Ratio (99% CI)	1.26 [0.84, 1.89]
22 SM free survival - advanced stages - sex	3	295	Peto Odds Ratio (99% CI)	0.92 [0.33, 2.56]
22.1 female patients	3	149	Peto Odds Ratio (99% CI)	1.43 [0.33, 6.27]
22.2 male patients	3	146	Peto Odds Ratio (99% CI)	0.62 [0.15, 2.54]
23 SM free survival - early stages - age	8	2921	Peto Odds Ratio (99% CI)	1.22 [0.89, 1.66]
23.1 0-15 years	4	55	Peto Odds Ratio (99% CI)	0.64 [0.16, 2.61]
23.2 16-39 years	8	2042	Peto Odds Ratio (99% CI)	1.35 [0.89, 2.04]
23.3 40-59 years	8	631	Peto Odds Ratio (99% CI)	0.96 [0.53, 1.76]
23.4 60+ years	6	193	Peto Odds Ratio (99% CI)	1.56 [0.68, 3.57]
24 SM free survival - advanced stages - age	3	277	Peto Odds Ratio (99% CI)	1.15 [0.40, 3.34]
24.1 16-39 years	3	210	Peto Odds Ratio (99% CI)	0.82 [0.26, 2.60]
24.2 40+ years	3	67	Peto Odds Ratio (99% CI)	8.17 [0.51, 130.56]
25 SM free survival - non-malignant skin cancers excluded	10	3221	Peto Odds Ratio (99% CI)	1.18 [0.87, 1.60]
25.1 early stages	8	2926	Peto Odds Ratio (99% CI)	1.18 [0.86, 1.62]
25.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	1.15 [0.40, 3.25]
26 SM before progression/relapse - non-malignant skin cancers excluded	10	3215	Peto Odds Ratio (99% CI)	1.45 [0.87, 2.43]
26.1 early stages	8	2920	Peto Odds Ratio (99% CI)	1.43 [0.84, 2.43]
26.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	1.77 [0.24, 13.11]
27 solid tumors	10	3221	Peto Odds Ratio (99% CI)	1.18 [0.83, 1.68]
27.1 early stages	8	2926	Peto Odds Ratio (99% CI)	1.26 [0.87, 1.81]
27.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	0.70 [0.23, 2.09]
28 solid tumors before progression/relapse	10	3215	Peto Odds Ratio (99% CI)	1.53 [0.89, 2.62]
28.1 early stages	8	2920	Peto Odds Ratio (99% CI)	1.53 [0.88, 2.67]
28.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	1.49 [0.17, 13.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29 solid tumors - non-malignant skin cancers excluded	10	3212	Peto Odds Ratio (99% CI)	1.20 [0.83, 1.73]
29.1 early stages	8	2917	Peto Odds Ratio (99% CI)	1.25 [0.84, 1.84]
29.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	0.86 [0.27, 2.68]
30 breast cancers	8	1531	Peto Odds Ratio (99% CI)	3.25 [1.06, 9.95]
30.1 early stages	8	1531	Peto Odds Ratio (99% CI)	3.25 [1.06, 9.95]
31 lung cancers	8	2926	Peto Odds Ratio (99% CI)	1.73 [0.72, 4.18]
31.1 early stages	8	2926	Peto Odds Ratio (99% CI)	1.73 [0.72, 4.18]
32 AML/MDS	10	3221	Peto Odds Ratio (99% CI)	1.62 [0.61, 4.33]
32.1 early stages	8	2926	Peto Odds Ratio (99% CI)	1.54 [0.57, 4.20]
32.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	5.81 [0.03, 1003.91]
33 NHL	10	3221	Peto Odds Ratio (99% CI)	0.85 [0.34, 2.13]
33.1 early stages	8	2926	Peto Odds Ratio (99% CI)	0.80 [0.31, 2.04]
33.2 advanced stages	3	295	Peto Odds Ratio (99% CI)	3.59 [0.05, 262.65]

Analysis 4.1. Comparison 4 IF-RT vs. EF-RT, Outcome 1 overall survival.

Analysis 4.2. Comparison 4 IF-RT vs. EF-RT, Outcome 2 OS - RT plus CT.

Analysis 4.3. Comparison 4 IF-RT vs. EF-RT, Outcome 3 OS - RT without CT.

Analysis 4.4. Comparison 4 IF-RT vs. EF-RT, Outcome 4 OS - early stages - sex.

Analysis 4.5. Comparison 4 IF-RT vs. EF-RT, Outcome 5 OS - advanced stages - sex.

Analysis 4.6. Comparison 4 IF-RT vs. EF-RT, Outcome 6 OS - early stages - age.

Study or subgroup	IF-RT n/N	EF-RT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Test for overall effect: $Z=0.45$ ($P=0.66$)					
Test for subgroup differences: $\text{Chi}^2=5.06$, $\text{df}=1$ ($P=0.17$), $I^2=40.72\%$					
<div style="display: flex; justify-content: space-between;"> Favours EF-RT Favours IF-RT </div>					

Analysis 4.7. Comparison 4 IF-RT vs. EF-RT, Outcome 7 OS - advanced stages - age.

Study or subgroup	IF-RT n/N	EF-RT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
4.7.1 16-39 years					
CALGB 6604	9/13	4/9		8.82%	0.66[0.15,2.99]
Obninsk, advanced	37/67	40/89		49.7%	0.65[0.34,1.22]
Stanf. H1, L1, L2	5/7	22/25		11.71%	1.72[0.47,6.37]
Subtotal (95% CI)	87	123		70.23%	0.76[0.51,1.15]
Total events: 51 (IF-RT), 66 (EF-RT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=3.09$, $\text{df}=2$ ($P=0.21$); $I^2=35.34\%$					
Test for overall effect: $Z=1.3$ ($P=0.19$)					
4.7.2 40+ years					
CALGB 6604	11/11	10/10		11.62%	0.8[0.22,2.96]
Obninsk, advanced	13/18	7/16		12.49%	0.37[0.1,1.31]
Stanf. H1, L1, L2	6/6	6/6		5.66%	0.69[0.11,4.51]
Subtotal (95% CI)	35	32		29.77%	0.56[0.3,1.05]
Total events: 30 (IF-RT), 23 (EF-RT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=1.29$, $\text{df}=2$ ($P=0.52$); $I^2=0\%$					
Test for overall effect: $Z=1.82$ ($P=0.07$)					
Total (95% CI)	122	155		100%	0.7[0.5,0.98]
Total events: 81 (IF-RT), 89 (EF-RT)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=5.04$, $\text{df}=5$ ($P=0.41$); $I^2=0.88\%$					
Test for overall effect: $Z=2.08$ ($P=0.04$)					
Test for subgroup differences: $\text{Chi}^2=0.66$, $\text{df}=1$ ($P=0.42$), $I^2=0\%$					
<div style="display: flex; justify-content: space-between;"> Favours EF-RT Favours IF-RT </div>					

Analysis 4.8. Comparison 4 IF-RT vs. EF-RT, Outcome 8 progression free survival.

Study or subgroup	IF-RT n/N	EF-RT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
4.8.1 early stages					
EORTC-GELA, H8U	97/660	42/324		19.35%	0.9[0.56,1.45]
GHSG, HD8	59/571	56/565		18.64%	0.95[0.58,1.54]
GPMC, EF-RT vs. IF-R	13/43	21/47		5.32%	1.56[0.63,3.89]
Lygra I	16/19	26/31		5.36%	1.2[0.49,2.99]
Milan, trial # 9005	6/70	3/66		1.49%	0.53[0.09,2.96]
Obninsk, R 18	18/78	40/157		8.44%	1.22[0.59,2.53]
Rome, HD 94	7/63	4/67		1.81%	0.51[0.11,2.45]
Stanf. H1, L1, L2	60/73	59/86		16.28%	0.61[0.36,1.03]
Subtotal (95% CI)	1577	1343		76.69%	0.9[0.75,1.08]
<div style="display: flex; justify-content: space-between;"> Favours EF-RT Favours IF-RT </div>

Analysis 4.9. Comparison 4 IF-RT vs. EF-RT, Outcome 9 PFS - censored at cut-off date.

Analysis 4.10. Comparison 4 IF-RT vs. EF-RT, Outcome 10 PFS - RT plus CT.

Analysis 4.11. Comparison 4 IF-RT vs. EF-RT, Outcome 11 PFS - RT without CT.

Analysis 4.12. Comparison 4 IF-RT vs. EF-RT, Outcome 12 PFS - early stages - sex.

Analysis 4.13. Comparison 4 IF-RT vs. EF-RT, Outcome 13 PFS - advanced stages - sex. **Analysis 4.14. Comparison 4 IF-RT vs. EF-RT, Outcome 14 PFS - early stages - age.**

Analysis 4.15. Comparison 4 IF-RT vs. EF-RT, Outcome 15 PFS - advanced stages - age.

Analysis 4.16. Comparison 4 IF-RT vs. EF-RT, Outcome 16 second malignancy free survival.

Analysis 4.17. Comparison 4 IF-RT vs. EF-RT, Outcome 17 SM free survival - censored at cut-off date.

Analysis 4.18. Comparison 4 IF-RT vs. EF-RT, Outcome 18 SM free survival - RT plus CT.

Analysis 4.19. Comparison 4 IF-RT vs. EF-RT, Outcome 19 SM free survival - RT without CT.

Analysis 4.20. Comparison 4 IF-RT vs. EF-RT, Outcome 20 SM before progression or relapse.

Analysis 4.21. Comparison 4 IF-RT vs. EF-RT, Outcome 21 SM free survival - early stages - sex.

Analysis 4.22. Comparison 4 IF-RT vs. EF-RT, Outcome 22 SM free survival - advanced stages - sex.

Analysis 4.23. Comparison 4 IF-RT vs. EF-RT, Outcome 23 SM free survival - early stages - age.

Analysis 4.24. Comparison 4 IF-RT vs. EF-RT, Outcome 24 SM free survival - advanced stages - age.

Study or subgroup	IF-RT n/N	EF-RT n/N	Peto Odds Ratio 99% CI	Weight	Peto Odds Ratio 99% CI
Test for subgroup differences: $\chi^2=2.24$, $df=1$ ($P=0.13$), $I^2=55.4\%$					
Favours EF-RT 0.01 0.1 1 10 100 Favours IF-RT					

Analysis 4.25. Comparison 4 IF-RT vs. EF-RT, Outcome 25 SM free survival - non-malignant skin cancers excluded. **Analysis 4.26. Comparison 4 IF-RT vs. EF-RT, Outcome 26 SM before progression/relapse - non-malignant skin cancers excluded.**

Analysis 4.27. Comparison 4 IF-RT vs. EF-RT, Outcome 27 solid tumors.

Analysis 4.28. Comparison 4 IF-RT vs. EF-RT, Outcome 28 solid tumors before progression/relapse.

Analysis 4.29. Comparison 4 IF-RT vs. EF-RT, Outcome 29 solid tumors - non-malignant skin cancers excluded.

Analysis 4.30. Comparison 4 IF-RT vs. EF-RT, Outcome 30 breast cancers.

Analysis 4.31. Comparison 4 IF-RT vs. EF-RT, Outcome 31 lung cancers.

Analysis 4.32. Comparison 4 IF-RT vs. EF-RT, Outcome 32 AML/MDS.

Analysis 4.33. Comparison 4 IF-RT vs. EF-RT, Outcome 33 NHL.

166

ADDITIONAL TABLES

Table 1. Previous SM investigations: All SM

publica- tion	char- acter- istics	number of SM	treatment groups	analysis methods	conclusions all SM	conclusions ST	conclusions AML	conclu- sions NHL
Abraham- sen 1993	1 cen- tre (Oslo); 1968-1985 MFU=8 yrs.; n=1152	N=68 (+6 ex- cluded non- melanoma skin cancers); 9 AML, 8 NHL, 51 ST	RT, CT, CT+RT; total treatment	Cox regression	Greater risk of SM for pts. who received both CT and RT			
Bhatia 1996	15 cen- tres (USA, Man- ches- ter, Am- ster- dam); 1955-1986; MFU=11.4 yrs.; n=1380 (chil- dren<16 yrs.)	N=88 (+9 ex- cluded non- melanoma skin cancers); 24 AML (+2 other leukemias), 47 ST, 9 NHL	RT, CT, RT+CT; total treatment	Cox regression sep- arately for ST, AML, NHL		all ST: no differ- ences; breast can- cer only: RT dose (RR 5.9 for dose > 20 Gy)	no differences reported	higher risk with more alkylating agents
Biti 1994	1 cen- tre (Flo- rence); 1960-1988 MFU=11.4 yrs.; n=1121	N=73 (+5 exclud- ed basocellular skin cancers); 60 ST, 11 AML (MDS excluded), 2 NHL	A. RT, CT, RT+CT, CRT; total treatment. B. RT, CT, CRT; primary treatment only, cen- sored at relapse	Cox regression	Higher risk after pri- mary CT compared with IF/M alone; high- er risk with CT + (S)T- NI compared with IF/M alone	Same trend as for all SM	Higher risk with primary CT (+/- RT); higher risk with more cy- cles of CT	
Boivin 1995	Em- bed- ded case- control study; 14 cen- tres; 1940-1987;	N=560; 403 ST, 122 AML, 35 NHL	RT, CT as time-de- pendent variables; primary and salvage RT, CT	Cox regression with splenectomy, RT, CT as time-depen- dent covariates		Significantly more with CT than with- out CT (ST and NHL analysed together)	Significantly more with CT than without CT (more with MOPP than with ABVD)	

Table 1. Previous SM investigations: All SM (Continued)

		MFU=7 yrs.; n=10472 (9280 fol- lowed for at least one year)						
Dietrich 1994	1 cen- tre (France); 1960-1983; n=892 (con- tinu- ous- ly dis- ease-free HD on- ly)	N=56 (first fu-year excluded); 37 ST (excluding bcc), 1960-1983; 11 ANLL/MDS, 8 NHL	RT vs. CRT; Man- tle-RT vs. EF-RT; SM before progres- sion/relapse only	Cox-regression; All RR compared with IF (=MF/inverted Y- RT)	Significant excess on- ly with MOPP+EF (RR 10.86, p<0.001) and MOPP+IF (RR 4.99, p = 0.015).	Same tendency as for SM, but signifi- cant only for MOPP +EF	Increased risk only for MOPP +EF (RR 16.55, p=.004)	No differ- ence in treatment
Dores 2002	16 US and Euro- pean cancer reg- istries; 1935-1995; n=32591	N=2153; 1726 ST, 169 ANLL, 162 NHL	RT vs. CT vs. CRT; pri- mary treatment	No explicit com- parison between treatment groups: all results as RR ac- cording to prima- ry treatment com- pared with normal population.		Significantly high- er RR with CRT (95%-CI 2.6-3.6) compared with either RT alone (2.1-2.4) or CT alone (1.5-1.9). Di- gestic tract and fe- male breast: Signif- icantly higher risks with RT than with- out RT.		
Mauch 1996	1 cen- tre (JCRT Boston, USA); 1969-1988; n=794	N=72; 53 ST, 8 AML, 10 NHL	RT(no relapse), RT- relapse-CT, CRT; total treatment	RRs compared with normal population, no direct treatment comparisons	RT alone RR 4.1, RT+CT RR 9.75, p<0.05	Same effect as with all SM	Same effect as with all SM	

Table 1. Previous SM investigations: All SM (Continued)

Ng 2002	4 centres (all af-fil. to Harvard); 1969-1997; MFU=12 yrs.; n=1319 (mainly early stages); (996 pts with fu > 10 years were included in analysis of treatment effect).	N=181 (N=162 for pts. with fu>10 yrs.); 131 ST, 23 AML, 24 NHL	RT, CRT. Total treatment, also separate analyses of nonrelapsed cases and relapsed cases	RRs calculated relative to normal population (age/sex-specific); CI from Poisson distrib.	RR higher with CRT than RT alone (6.1 vs. 4.0, p=0.015); (non-relapsed cases only: 5.9 vs. 3.7, p=0.016). Analysed by radiation field size, this effect was only significant for TNI (+/-CT). RR higher with CT + TNI than for CT + Mantle/EF.		
Rodriguez 1993	1 centre (M.D. Anderson, Houston, USA); 1966-1987; n=1013	N=66 (first fu-year excluded); 38 ST, 14 AML/MDS, 14 NHL	IF vs. EF (+MOPP); CT vs. CRT; RT vs. CRT. Total therapy	Cox's proportional hazards model for risk-factors	RT vs. CRT: no difference (p=0.37). CT vs. CRT: less SM with CRT (p=0.001). But less courses of CT with CRT than with CT only!		
Swerdlow 1992	>60 BNLI centers, UK;	N=113; 80 ST, 16 AML, 17 NHL	Alkyl. CT, Alkyl. CT +RT, IF-RT (+/- nonalk. CT), EF-RT (+/- nonalk. CT). Total treatment	Poisson regression	No difference overall (nor for lung ca. alone)	More with CT or CRT (similar) than with RT	No differences

Table 1. Previous SM investigations: All SM (Continued)

1970-1987; n=2846								
Swerdlow 2000	BNLI, Royal Mars- den, St. Bartholomews; 1963-1993; n=5519	N=322; 228 ST, 44 AML, 50 NHL	CT, RT, CRT. Total treatment	Poisson regression. RR compared with normal population; no direct treatment comparisons.	Higher RR for CRT (SIR 3.9, 95% CI 3.2 - 4.6) than for CT (SIR 2.6, 95% CI 2.1 - 3.2) or RT (SIR 2.3, 95% CI 1.9 - 2.8).		Higher risk for CRT (SIR 38.1, 95% CI 24.6 - 55.9) or CT (SIR 31.6, 95% CI 19.7 - 47.6) than for RT (SIR 1.2, 95% CI 0.1 - 5.2)	No signif- icant dif- ferences.
Tucker 1988	Stan- ford UMC; 1968 - ?; n=1507	N=83 (first fu-year excluded); 46 ST, 28 AML, 9 NHL	RT, RT+adj. CT, RT +salvage CT, RT+in- travenous-gold, CT. Total treatment	Kaplan-Meier, Gehan test		No differences (ex- cept: more with ra- diotherapy+intra- venous-gold)	more with CT than RT	No differ- ences
van Leeu- ven 1994	2 cen- ters (Nether- lands); 1966-1986; MFU=9 yrs.; n=1939	N=146; 93 ST, 31 AML, 23 NHL	CT, RT, CRT. Total treatment	A. Person-years analysis. B. Cox re- gression		B: for lung cancer only: trend to more for RT (p=0.08) or CRT (p=0.07) than for CT. Otherwise no differences	A: AML not in- creased for RT; large increase for CT (CT sim- ilar to CRT). B: AML more for CT (p=0.009) or CRT (p=0.04) than for RT	B: trend to more for CRT than for either CT or RT (p=0.06)

Table 2. Previous SM investigations: solid tumors and NHL

Publication	Characteristics	Number of ST	Treatment groups	Analysis methods	conclusions ST	conclusions NHL
Birdwell 1997	Stanford UMC (USA); 1961-1994; MFU=10.9 yrs.; n=2441	25 gastrointestinal cancers	RT, CRT. Total treatment	RR compared with general population. No direct treatment comparisons.	Risk of gastrointestinal cancer not significantly greater with CRT (RR 3.9, 95%CI 2.2-5.6) than with RT (RR 2.0, CI 1.0-3.4)	
Enrici 1998	One centre (Rome); 1972-1996; MFU=84 months; n=391	20 NHL	A. RT, CT, CRT - initials treatment, censored at relapse. B. RT, CT, CRT - total treatment.	Kaplan-Meier and Cox regression		No difference between treatment modalities
Hancock 1993	Stanford UMC (USA); 1961-1990; MFU=10 yrs.; n=885	25 breast cancers	RT, CRT. Total treatment	RR compared with general population. No direct treatment comparisons.	RT vs. CRT: Tendency of more breast cancers with CRT, but not significant. RT: RR 3.5 (95% CI 1.9-5.8), CRT: RR 5.7 (95% CI 3.1-9.5).	
Swerdlow 2001	Nested case-control study; multi-centre (Britain); 1963-1995; n=5519	88 lung cancers	RT, CT, CRT. Total treatment	conditional logistic regression	No significant differences in lung cancer risk between RT, CT, CRT. (exception: adenocarcinomas - greater risk with CT than without.) Risk greater with MOPP than without MOPP	
van Leeuwen 1995	Embedded case-control study; 2 centres (Netherlands); 1966-1986; n=1939	30 lung cancers	RT, CT, CRT. RT dose to lung. Total treatment	conditional logistic regression	Risk of lung cancer tended to increase with increasing RT dose (p=0.01); RR(>9 Gy vs. 0) = 9.6. No significant differences between RT, CT, CRT	

Table 3. Previous SM investigations: AML/MDS

Publication	Characteristics	Number of AML/MDS	Treatment groups	Analysis methods	Conclusions AML
Brusamolino 1998	2 centres (Italy); 1975-1992; MFU=10 yrs.; n=1659	36 AML/MDS	RT, CT, CT +RT. Total treatment	A. Log-rank tests (univariate) to compare treatment groups B. Embedded case-control study with conditional logistic regression analysis.	A. Higher risk after CT than RT (p=0.04); higher risk with CT than with CRT (p=0.05); higher risk with MOPP+RT than with MOPP/ABVD or with ABVD+RT (p=0.002); higher risk with EF + MOPP than with IF+MOPP (p=0.01) B. higher risk after CT than RT (OR 4.1; p=0.05); higher risk after CRT than RT (OR 6.4; p=0.02); higher risk after MOPP+RT

Table 3. Previous SM investigations: AML/MDS (Continued)

					than ABVD+RT (OR 5.9; p=0.001) or MOPP/ABVD
Josting 2003	Retrospective analysis; multi-centre (GHSG (Germany) HD1-HD9); 1981-1998; MFU=55 months; n=5411	46 AML/MDS	CT, RT, CRT, HDCT with SCT. Primary treatment, not censored at relapse	Kaplan-Meier. No direct treatment comparison.	No significant differences between treatment protocols.
Kaldor 1990	Case-control study; 12 cancer registries (Europe, Canada), 6 large hospitals (Europe); 1960-?; n=29552	149 AL/NLL/MDS (at least one year after HD diagnosis)	RT, CT, CRT. Total treatment	Standard case-control study methods. RR compared with RT.	Higher risk with CT than with RT (RR 9.0; CI 4.1-20); higher risk with CRT than with RT (RR 7.7; CI 3.9-15). No difference in CT vs. CRT; but there was a dose-related increase in the risk in pts who received RT alone.
Pedersen-Bjergaard 1987	1 centre (Copenhagen); 1970-1981; n=391	20 AN-LL/preleukemia	low, intermediate, or high dose of alkylating agents. Total treatment	Cox regression	Risk increases with increasing (total) log dose of alkylating agents (p=0.0024, regr. coefft.=0.69)
van Leeuwen 1994b	Embedded case-control study; 2 centres (Netherlands); 1966-1986; n=1939	44 Leukemias (incl. 32 ANLL, 12 MDS)	RT, CT, RT +CT. Total treatment	conditional logistic regression	More risk with CT than with RT alone; ≤6 cycles: p=0.08, RR=8.5; >6 cycles: p<0.001, RR=44

Table 4. RT vs. CRT, early stages: Peto estimated rates (%)

years since SPT	pts. at risk for SM	no. of tri-als	OS (RT : CRT)	PFS (RT : CRT)	SM (RT : CRT)	ST (RT : CRT)	AML (RT : CRT)	NHL (RT : CRT)
5	1536 : 1517	13	92 : 94	68 : 89	2 : 2	1 : 1	0 : 1	1 : 0
10	1150 : 1173	13	83 : 90	61 : 82	5 : 5	3 : 3	1 : 1	1 : 1
15	551 : 584	11	78 : 82	56 : 73	11 : 9	8 : 7	1 : 2	2 : 1
20	343 : 356	9	69 : 75	52 : 66	18 : 15	14 : 12	1 : 2	3 : 1
25	202 : 215	7	61 : 70	47 : 62	26 : 21	23 : 18	1 : 2	3 : 1
30	85 : 103	6	58 : 67	45 : 56	33 : 24	29 : 21	1 : 2	3 : 1
30+	6 : 12	2	37 : 65	25 : 53	33 : 24	29 : 21	1 : 2	3 : 1

Table 5. RT vs. CRT, advanced stages: Peto estimated rates (%)

years since SPT	pts. at risk for SM	no. of tri-als	OS (RT : CRT)	PFS (RT : CRT)	SM (RT : CRT)	ST (RT : CRT)	AML (RT : CRT)	NHL (RT : CRT)
5	114 : 175	3	68 : 64	33 : 51	4 : 1	4 : 1	too few cases	too few cases
10	75 : 109	3	54 : 56	30 : 44	12 : 4	10 : 1		
15	56 : 90	3	47 : 46	28 : 36	18 : 9	16 : 7		
20	37 : 64	3	38 : 40	22 : 32	22 : 12	18 : 10		
25	18 : 34	3	36 : 32	21 : 26	41 : 17	32 : 15		
30	8 : 13	2	6 : 29	2 : 24	49 : 30	40 : 38		

Table 6. CT vs. CRT, early stages: Peto estimated rates (%).

years after SPT	pts at risk for SM	no of trials	OS (CT : CRT)	PFS (CT : CRT)	SM (CT : CRT)	ST (CT : CRT)	AML (CT : CRT)	NHL (CT : CRT)
5	263 : 276	4	84 : 90	66 : 79	1 : 1	1 : 1	0 : 0	0 : 1
10	240 : 260	4	73 : 85	54 : 71	2 : 3	2 : 2	0 : 1	1 : 1
15	138 : 160	4	69 : 80	50 : 66	4 : 4	2 : 3	0 : 1	2 : 1
20	56 : 96	3	69 : 78	49 : 64	4 : 4	2 : 3	0 : 1	2 : 1
25	5 : 7	1	69 : 78	49 : 64	4 : 4	2 : 3	0 : 1	2 : 1

Table 7. CT vs. CRT, advanced stages: Peto estimated rates (%)

years after SPT	pts. at risk for SM	no. of trials	OS (CT : CRT)	PFS (CT : CRT)	SM (CT : CRT)	ST (CT : CRT)	AML (CT : CRT)	NHL (CT : CRT)
5	674 : 804	13	74 : 76	56 : 63	2 : 4	1 : 1	1 : 2	0 : 1
10	593 : 721	13	66 : 65	50 : 56	4 : 8	2 : 4	1 : 2	1 : 1
15	311 : 406	13	59 : 60	47 : 52	6 : 10	3 : 6	1 : 2	1 : 1
20	152 : 216	10	51 : 55	43 : 50	12 : 12	8 : 8	2 : 3	2 : 3
25	51 : 98	10	48 : 48	38 : 45	20 : 15	15 : 10	2 : 3	2 : 3
30	20 : 28	5	44 : 45	34 : 35	23 : 24	18 : 20	2 : 3	2 : 3

Table 8. RT vs. CT, early stages: Peto estimated rates (%)

years since SPT	pts. at risk for SM	no. of tri-als	OS (RT : CT)	PFS (RT : CT)	SM (RT : CT)
5	154 : 145	2	86 : 83	67 : 68	0 : 2
10	133 : 121	2	65 : 66	53 : 52	1 : 8
15	97 : 83	2	62 : 61	48 : 48	1 : 8
20	79 : 49	2	58 : 59	45 : 46	5 : 10
25	15 : 2	1	45 : 55	35 : 43	15 : 13

Table 9. RT vs. CT, advanced stages: Peto estimated rates (%)

years since SPT	pts. at risk for SM	no. of tri-als	OS (RT : CT)	PFS (RT : CT)	SM (RT : CT)
5	53 : 63	1	75 : 63	42 : 42	1 : 7
10	38 : 37	1	67 : 51	39 : 38	5 : 7
15	31 : 29	1	61 : 47	36 : 37	5 : 7
20	19 : 23	1	56 : 37	32 : 31	11 : 8
25	6 : 5	1	56 : 37	32 : 31	32 : 11

Table 10. IF vs. EF, early stages: Peto estimated rates (%)

years since SPT	pts. at risk for SM	no. of trials	OS (IF : EF)	PFS (IF : EF)	SM (IF : EF)	ST (IF : EF)	AML/MDS (IF : EF)	NHL (IF : EF)
5	1579 : 1279	8	92 : 92	86 : 88	2 : 3	1 : 1	1 : 1	0 : 1
10	967 : 776	8	89 : 88	82 : 84	4 : 4	2 : 2	1 : 2	1 : 1
15	178 : 194	6	84 : 81	78 : 79	7 : 8	5 : 5	1 : 2	2 : 1
20	141 : 140	4	74 : 72	71 : 69	17 : 19	11 : 17	1 : 2	6 : 2
25	90 : 100	4	66 : 66	66 : 64	22 : 31	16 : 27	1 : 3	6 : 2
30	35 : 43	4	50 : 52	54 : 53	29 : 37	23 : 32	1 : 3	6 : 6
30+	22 : 21	2	45 : 44	42 : 38	43 : 42	34 : 36	1 : 3	10 : 6

Table 11. IF vs. EF, advanced stages: Peto estimated rates (%)

years since SPT	pts. at risk for SM	no. of trials	OS (IF : EF)	PFS (IF : EF)	SM (IF : EF)	ST (IF : EF)	AML/MDS (IF : EF)	NHL (IF : EF)
5	125 : 170	3	55 : 73	33 : 55	0 : 2	0 : 1	0 : 1	0 : 0
10	68 : 121	3	44 : 63	28 : 49	2 : 3	2 : 2	0 : 1	0 : 0
15	45 : 87	3	36 : 56	26 : 45	7 : 5	6 : 4	0 : 1	0 : 1
20	28 : 55	3	31 : 48	23 : 42	20 : 10	20 : 8	0 : 1	0 : 1
25	15 : 39	3	27 : 38	22 : 34	23 : 19	22 : 14	0 : 1	1 : 5
30	6 : 16	3	26 : 17	21 : 29	24 : 27	24 : 22	0 : 1	1 : 5

WHAT'S NEW

Date	Event	Description
29 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

FRANKLIN, JEREMY: write protocol, supervise selection of trials and data collection, perform statistical analyses, chair collaborators' meetings, write review

PAUS, MARCUS: search for and select trials, contact trialists, research medical aspects, organise collaborators' meetings

PLUETSCHOW, ANNETTE: check and correct IPD, perform statistical analyses, present results for collaborators' meetings, write review

SPECHT, LENA: assist in contacting trialists, advise on methodology, interpret results

DECLARATIONS OF INTEREST

There is no known conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Klinik I für Innere Medizin, Cologne University, Germany.

External sources

- Deutsche Forschungs-Gemeinschaft (DFG), Germany.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [adverse effects]; Combined Modality Therapy; Hodgkin Disease [*drug therapy] [*radiotherapy]; Neoplasms, Radiation-Induced [*etiology]; Neoplasms, Second Primary [chemically induced] [*etiology]; Randomized Controlled Trials as Topic; Risk Assessment

MeSH check words

Humans