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TITLE: Role of chemotherapy in 5 000 patients with head and neck cancer treated by curative surgery: a subgroup analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer

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1 **TITLE: Role of chemotherapy in 5 000 patients with head and neck cancer treated by curative surgery:**
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3

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9

10 **ABSTRACT**

11 **Objective:** To evaluate the effect of chemotherapy added to a surgical locoregional treatment (LRT) for
12 patients with locally advanced head and neck squamous cell carcinoma (HNSCC).

13 **Materials and Methods:** We studied the sub-group of trials with surgical LRT included in the meta-
14 analysis on chemotherapy in head and neck cancer (MACH-NC). Data from published and unpublished
15 randomized trials comparing the addition of chemotherapy to LRT in HNSCC patients were sought using
16 electronic database searching for the period 1965-2000, hand searching and by contacting experts in the
17 field. Trials with less than 60 patients, or preoperative radiotherapy or where the type of LRT could not
18 be individually determined were excluded. All individual patient data were checked for internal
19 consistency, compared with published reports, and validated with trialists. Data were pooled using a
20 fixed-effect model. Heterogeneity was assessed using Cochrane test and I^2 statistics.

21 **Results:** Twenty-four trials were eligible (5000 patients). Chemotherapy improved overall survival
22 (HR=0.92 [95%CI: 0.85 to 0.99] p=0.02). There was a significant interaction between treatment effect
23 and timing of chemotherapy (p=0.08 at pre-specified threshold of 0.1) with a greater effect for
24 concomitant chemotherapy (HR=0.79, 95%CI: 0.69 to 0.92). The benefit of chemotherapy was greater in
25 women (HR_{women}=0.63, 95%CI: 0.50 to 0.80) compared to men (HR_{men}=0.96, 95%CI: 0.89 to 1.04; p for
26 interaction =0.001).

27 **Conclusions:** This analysis confirmed the benefit of concomitant chemotherapy added to surgical LRT.
28 The role of induction therapy as yet to be determined as it did not improve OS. Women may benefit
29 more than men from chemotherapy.

30 **Key word:** head and neck cancer, squamous cell carcinoma, chemotherapy, surgery, meta-analysis,
31 individual patient data, randomized trial

32 **Highlights (3-5)**

33 Addition of chemotherapy to surgery improved overall survival in head & neck cancer.

34 Improvement of overall survival was greater with concomitant chemotherapy.

35 Induction chemotherapy did not significantly improved overall survival

36 Women benefited from chemotherapy more than men.

37 Effect of sex on survival should be investigated more in head and neck cancer.

38

39 **Conflict Of Interest statement**

40 None declared

41

42 **Abbreviations**

43 **HNSCC : Head and neck Squamous cell carcinoma**

44 **HR: Hazard Ratio**

45 **95%CI: 95% Confidence interval**

46 **IPD: Individual patient data**

47 **LRT: Locoregional Treatment**

48 **OS: Overall survival**

49 **MACH-NC: Meta-analysis of Chemotherapy in Head and Neck Cancer**

50 **INTRODUCTION**

51 Every year, more than 600 000 patients are diagnosed with head and neck cancer worldwide¹. Most of
52 these cancers are squamous cell carcinomas (HNSCC); half of them diagnosed at locally advanced stage².
53 In the individual patient data (IPD) meta-analysis of randomized clinical trials MACH-NC (Meta-analysis of
54 Chemotherapy in Head and Neck Cancer), we showed that the addition of chemotherapy to locoregional
55 treatment (LRT) improved overall survival (OS) in locally advanced non-metastatic HNSCC³. This meta-
56 analysis of 87 trials completed between 1965 and 2000 included 16 485 patients. Hazard ratio (HR) for
57 death was 0.88 (95% confidence interval (95%CI): 0.85 to 0.92; $p < .001$) with an absolute benefit on
58 survival of 4.5% at 5 years. Benefit was significantly more pronounced for chemotherapy concomitant to
59 radiotherapy with a 6.5% benefit at 5 years (HR=0.81, 95%CI 0.78 to 0.86). In this meta-analysis, patients
60 treated by surgery, radiotherapy, or both were analyzed together. However, patients' characteristics
61 usually differ between trials that included patients treated by surgery as primary LRT and trials that
62 included patients treated by radiotherapy only. For example, in a study on oral cavity cancer, patients
63 treated by surgery were younger and had lower stage cancer⁴. In a preliminary analysis of the MACH-NC
64 database, we compared patients treated by surgery (+/- radiotherapy) to patients treated by
65 radiotherapy only. Among the patients included in this preliminary analysis (eTable 1), 5 352 (32.9 %) had
66 surgery as LRT. These patients had lower stage tumors (48% stage IV versus 65% for radiotherapy
67 patients; $p < .001$) and had oral cavity tumors more frequently (33% versus 21% for radiotherapy patients;
68 $p < .001$). Age, sex, and performance status were also significantly different. Forty per cent of patients
69 treated by surgery received induction chemotherapy whereas only 21% of patients treated by
70 radiotherapy did. Because patients treated by surgery are different, the effect of chemotherapy and its
71 interaction with patient characteristics on their survival might vary. Moreover the addition of surgery in
72 LRT changes the adverse events patients may encounter and modifies the timing of radiotherapy. Finally,
73 although the MACH-NC meta-analysis showed no effect of induction therapy on survival, the use of

74 induction chemotherapy is still debated, especially when surgery is considered for LRT⁵⁻⁷. Thus, it was
75 decided to perform a specific analysis of patients treated by surgery in the MACH-NC database.

76 The primary objective was to evaluate the benefit on overall survival of chemotherapy in addition to a
77 surgical LRT for patients diagnosed with locally advanced HNSCC. There were two secondary objectives:
78 first, to investigate interaction between the effect of chemotherapy and patient or trial characteristics;
79 and second, to study event-free survival and the different types of failure.

80 **METHODS**

81 The protocol for this meta-analysis was redacted prior to the analysis and is available at:

82 https://www.gustaveroussy.fr/sites/default/files/protocol_mach_nc_surg.pdf

83 Trial selection

84 This meta-analysis studied the subgroup of patients treated by surgery in the MACH-NC database.
85 Selection of included trials was described in previous publications³. All trials had to include previously
86 untreated patients with locally advanced non-metastatic HNSCC. Accrual had to be completed between
87 1965 and 2000. Trials had to use a randomization method that precluded prior knowledge of treatment
88 assignment. To be eligible in this analysis, trials had to compare curative surgical LRT (+/- radiotherapy)
89 versus the addition of chemotherapy to the same LRT. The timing of chemotherapy could be before
90 surgery (induction), during post-operative radiotherapy (concomitant) or after the end of the LRT
91 (adjuvant). Trials with less than 60 patients or with systematic preoperative radiotherapy were excluded.
92 Trials in which the patients could be treated by surgery (+/- radiotherapy) or radiotherapy alone, and in
93 which the type of LRT could not be individually determined were excluded, except if more than 50% of
94 patients had surgery. Both published and unpublished trials were included.

95 Data collection and consistency checking

96 The data collected for each patient were: age, sex, tumor stage, tumor site, performance status,
97 treatment allocated, survival and failure status, date of randomization, date of first failure, date of death
98 or date of last follow up. Information retrieved for each trial was: the timing of chemotherapy, the type
99 of chemotherapy (number and type of drugs), and the neck dissection strategy. For induction trials,
100 information on surgical margins strategy, planned number of chemotherapy cycles and possibility of
101 early LRT for non-responding patients was also collected. All IPD were checked with a standard
102 procedure^{3,8,9}, which follows the recommendations of the Cochrane working group on meta-analysis
103 using IPD. Results were compared with protocol (when available) and published reports, and validated
104 with the corresponding trialist.

105 Outcomes

106 Primary endpoint was overall survival (OS), defined as the time from randomization to death from any
107 cause. Secondary endpoints were early death and event-free survival. Death was considered early when
108 it occurred within 6 months after randomization. Event-free survival was defined as the time from
109 randomization to the first event¹⁰ (locoregional failure, distant failure, or death from any cause). Living
110 patients that presented no event were censored at their date of last follow up. Events considered as
111 locoregional failures were local failure, regional failure, or concomitant local and regional failure without
112 concomitant distant failure. Events considered as distant failure were distant failure, either alone or
113 combined with local or regional failure. Events considered as death without failure were death without
114 previous locoregional or distant event.

115 Statistical Analysis

116 All randomized patients were included in an intent-to-treat analysis. Median follow up was calculated
117 with the reverse Kaplan-Meier method¹¹. Analyses were stratified by trial. We calculated trial and overall
118 pooled hazard ratios (HR) using the log-rank expected number of events and variance, using a fixed

119 effect model. Stratified survival curves were computed for control and experimental groups using Peto's
120 method and were used to calculate absolute benefit at 5 years^{12,13}. Heterogeneity of chemotherapy
121 effect among trials was assessed using χ^2 heterogeneity test and I^2 statistic¹⁴. Because heterogeneity
122 test is not powerful, we chose a 0.10 significance threshold¹⁵. In case of significant heterogeneity, we
123 performed sensitivity analysis to identify the source of heterogeneity. If heterogeneity was still
124 significant and unexplained, we used a random-effect model^{15,16}.

125 Three sensitivity analyses were planned by exclusion of some trials: with less than 100 patients, with a
126 median follow up <5 years, and whose accrual period began before 1980. We also conducted a post hoc
127 analysis where outlier trials (trials that had a 95%CI that did not overlap with the 95%CI of the global HR)
128 were excluded.

129 In subset analyses, we used χ^2 heterogeneity tests among different groups of trials to study interaction
130 between trial characteristics and treatment effect. The residual heterogeneity within trial subgroups was
131 the difference between the overall χ^2 heterogeneity statistics and the χ^2 heterogeneity statistic
132 between groups¹⁷. Trial subsets were predefined according to: timing of chemotherapy, type of
133 chemotherapy drugs, and neck dissection strategy (not performed because of high rate of missing data);
134 for induction trials, surgical margins strategy, type of induction protocol (number of cycles, possibility of
135 early LRT). We performed two post hoc analyses: the first studied the type of chemotherapy in induction
136 trials and the second, the administration of radiotherapy in adjuvant trials. We investigated interaction
137 between treatment effect and patients characteristics (age, stage, sex, performance status, and primary
138 site of tumor) in a Cox model stratified by trial that included treatment arm, covariate and interaction.

139 Trials in these analyses had to include patients in all categories of the variable under study. In case of
140 significant interaction, the results were confirmed in a multivariate model including the other individual
141 characteristics. Since only the first event was collected in the meta-analysis, locoregional failure, distant
142 failure, and death without failure were analyzed using Fine and Gray models (unplanned competing risk

143 analysis)^{18,19}. Analyses were done using SAS, version 9.4 and RStudio (“*crrsc*” package for competing risk
144 analysis), version 3.2.5.

145 Role of the funding source

146 The sponsors of this study had no role in the study design, data collection, data analysis, data
147 interpretation, or in the writing of the report.

148 **RESULTS**

149 Population

150 Among the 87 trials included in MACH-NC database we identified 39 that proposed a surgical LRT. Fifteen
151 of those met predefined exclusion criteria (eFigure 1). The meta-analysis included 24 trials^{20–43} (5 000
152 patients) evaluating surgical LRT versus the same LRT + chemotherapy (eTable2). One trial (UKHAN-1⁴³)
153 had two strata comparisons based on the type of chemotherapy and was considered above as two
154 distinct trials. There were 7 adjuvant chemotherapy trials (1 743 patients), 11 induction chemotherapy
155 trials (1 925 patients) and 6 concomitant trials (1 332 patients). Two trials were unpublished (BNH003²⁹,
156 EORTC 24844³²) and two were published as abstracts only (AHNTG²⁷, GETTECadj²⁰). Postoperative
157 radiotherapy was planned in most of trials. Five adjuvant trials^{21,23–26} had only surgery as LRT (933/1 743
158 patients of adjuvant trials). Overall median follow up was 4.9 years (range: 1.3 to 13.7 years). Description
159 of the overall population is available in eTable 3. Number of events in each arm is given for all endpoints
160 in eTable 4.

161 Overall survival and event-free survival

162 There were 2 696 deaths. Chemotherapy improved OS (HR=0.92 [95%CI: 0.85 to 0.99] p=0.02, figure 1),
163 with an absolute benefit of 4.4% (95%CI: 1.3 to 7.5%) at 5 years (figure 2). There was a significant
164 interaction between treatment effect and timing of chemotherapy (p=0.08 at pre-specified threshold of

165 0.10) with a greater effect for concomitant chemotherapy (HR=0.79, 95%CI: 0.69 to 0.92) than for
166 induction (HR=0.96, 95%CI: 0.85 to 1.08) or adjuvant chemotherapy (HR=0.98, 95%CI: 0.85 to 1.12).
167 Heterogeneity was significant but moderate ($I^2=35\%$; $p=0.04$). Results of sensitivity analyses showed
168 similar results for treatment effect and heterogeneity (eTable 5), except for the one based on trials with
169 follow-up longer than 5 years (p for treatment effect =0.40) and the post-hoc analysis excluding two
170 outlier trials previously identified⁴⁴ (GETTECadj²⁰ and Toulouse³⁸; p for heterogeneity =0.39).
171 For event-free survival, based on 23 trials and 4 501 patients (2 659 events), similar results were
172 observed (eFigure 2), with an overall HR of 0.90 (95%CI: 0.84 to 0.98; $p=0.01$) and an absolute benefit of
173 3.3% (95%CI: 0.1 to 6.5%) at 5 years (eFigure 3). There was a significant interaction between treatment
174 effect and timing of chemotherapy ($p=0.05$) with a greater effect for concomitant chemotherapy
175 (HR=0.78, 95%CI: 0.68 to 0.90) than for induction (HR=0.98, 95%CI: 0.88 to 1.10) and adjuvant
176 chemotherapy (HR=0.91, 95%CI: 0.78 to 1.07). Heterogeneity was also significant ($I^2=46\%$, p for
177 heterogeneity =0.03).
178 Within 6 months after randomization, 323 deaths occurred. Overall HR for the effect of chemotherapy
179 on early death was 1.21 (95%CI: 0.97 to 1.51, $p=0.08$) without significant difference between
180 concomitant chemotherapy (HR=0.98, 95%CI: 0.65 to 1.47), induction therapy (HR=1.36, 95%CI: 0.96 to
181 1.94), or adjuvant chemotherapy (HR=1.28, 95%CI: 0.87 to 1.90; p for interaction =0.45, eFigure 4).

182 Subset analyses

183 The effect of chemotherapy on OS was significantly different according to the type of chemotherapy (p
184 for interaction =0.02): the HR was 0.74 (95%CI: 0.62 to 0.88) for platinum alone, 0.88 (95%CI: 0.76 to
185 1.02) for poly-chemotherapies based on platinum and 5-Fluorouracil (PF), 0.90 (95%CI: 0.74 to 1.11) for
186 other mono-chemotherapies and 1.04 (95%CI: 0.92 to 1.17) for other poly-chemotherapies. The benefit
187 of PF based chemotherapy was not significant in induction trials alone (eTable 6). No significant
188 interaction was observed between chemotherapy effect and the type of induction protocol, or the

189 strategy adopted for surgical margins (margin before any treatment vs. not specified) in induction trials
190 or modalities of LRT (surgery vs. surgery + RT) for adjuvant trials.

191 Sub-group analyses

192 A significant interaction between chemotherapy effect and patients' sex was found (Figure 3). Benefit of
193 chemotherapy on OS was greater for women ($HR_{\text{women}}=0.63$, 95%CI: 0.50 to 0.80) than for men
194 ($HR_{\text{men}}=0.96$, 95%CI: 0.89 to 1.04; p for interaction $<.001$). Heterogeneity of interaction between
195 treatment and sex was not significant (p for heterogeneity $=0.81$, eFigure5 and eTable7). Event-free
196 survival showed similar results ($HR_{\text{women}}=0.63$ (95%CI: 0.50 to 0.80) versus $HR_{\text{men}}=0.95$ (95%CI: 0.87 to
197 1.03); p for interaction $=0.001$).

198 The 718 (14%) women included in this study differed from the 4 262 (85%) men in age (younger), stage
199 (lower), performance status (better) and tumor site (more oral cavity, eTable 8). As all these covariates
200 significantly influenced survival (eTable 9), a multivariate interaction model adjusted on age, site and
201 stage was implemented and confirmed a significant interaction ($HR_{\text{women}}=0.62$ (95%CI: 0.49 to 0.79),
202 versus $HR_{\text{men}}=0.96$ (95%CI: 0.88 to 1.04); p for interaction $<.001$). Performance status was not included
203 because of missing data, but a sensitivity analysis including this covariate leads to similar results
204 ($HR_{\text{women}}=0.59$ (95%CI: 0.45 to 0.77), versus $HR_{\text{men}}=0.99$ (95%CI: 0.89 to 1.09); p for interaction $<.001$).
205 Absolute benefit at 5 years was 13.3% (95%CI: 9.1 to 17.5%) for women and 3.0% (95%CI: -0.6 to 6.4%)
206 for men (figure 4). A leave-one-out sensitivity analysis (post hoc analysis, eFigure 6), showed that the
207 RTOG 9501⁴² trial influenced interaction more than other trials. After exclusion of the RTOG trial⁴²,
208 interaction was still significant ($HR_{\text{women}}=0.69$ (95%CI: 0.54 to 0.89) versus $HR_{\text{men}}=0.95$ (95%CI: 0.88 to
209 1.04); p for interaction $=0.02$).

210 Patterns of failure

211 Because two trials had no information on locations of failures (Int0034²² and JHCFUS²³), only 4 291
212 patients were included in the failure analysis (eTable 4). Chemotherapy decreased significantly the
213 incidence of locoregional failure (HR=0.80, 95%CI: 0.70 to 0.90; p<.001) (Figure 5) but the decrease was
214 not significant for distant failure (HR=0.87, 95%CI: 0.75 to 1.00; p=0.06). Patients treated with
215 chemotherapy died without failure more than non-treated patients (HR=1.20, 95%CI: 1.06 to 1.37;
216 p=0.01). Patterns of failure were different between the different chemotherapy timing, particularly on
217 locoregional failure: significant benefit in concomitant and adjuvant trials but not on induction trials
218 (Figure5, eTable 10). Effect of chemotherapy on distant failure was non-significant for the three
219 chemotherapy timings.

220 Men and women had significantly different hazards for death without failure (HR_{women}=0.78 (95%CI: 0.53
221 to 1.15) versus HR_{men}=1.26 (95%CI: 1.10 to 1.45); p for interaction =0.02). Differences were not
222 significant for locoregional failure (HR_{women}=0.66 (95%CI=0.46 to 0.94) versus HR_{men}=0.82 (95%CI: 0.72 to
223 0.94); p for interaction =0.26) or for distant failure (HR_{women}=0.66 (95%CI: 0.46 to 1.11) versus HR_{men}=0.82
224 (95%CI: 0.77 to 1.04; p for interaction =0.35).

225 **DISCUSSION**

226 This meta-analysis on individual patient data is the first to investigate the effect of chemotherapy added
227 to surgical locoregional treatment (LRT) in HNSCC. The results confirmed those obtained in the MACH-NC
228 overall analysis³. The addition of chemotherapy to LRT improved patients' survival. Interaction with
229 chemotherapy timing was significant and a benefit was particularly observed for concomitant
230 chemotherapy.

231 Heterogeneity in our analysis was moderate ($I^2=35\%$). A major source of heterogeneity came from two
232 French trials: GETTECad²⁰ and Toulouse³⁸. Both trials selected patients with very high risk of failure as
233 they only included patients with invaded surgical margins and extra capsular invasion of cervical lymph

234 nodes. Both trials were already pointed out as heterogeneous trials in a previous work on heterogeneity
235 in the MACH-NC database⁴⁴. As we had limited information on toxicity, early deaths were analyzed as a
236 proxy of drug induced mortality, including potential impact on postoperative mortality but no significant
237 difference was found.

238 The effect of chemotherapy was consistent in all sensitivity analyses (except for trials with long follow-
239 up), as in analyses on event-free survival. The unplanned competing risk analysis suggested that
240 chemotherapy was most effective on locoregional failure. It showed that, for all chemotherapy timings,
241 treatment effect on distant failure was not significant. Mono-chemotherapy using platinum increased
242 patients' survival more than other chemotherapies. Interaction between chemotherapy and
243 radiotherapy by comparing the subset of trials with surgery and the subset of trials with surgery plus
244 radiotherapy could be investigated only in adjuvant subset as the induction subset did not include trials
245 with surgery alone: the interaction was not significant. Moreover, sensitivity analysis based only on trials
246 with surgery plus radiotherapy (excluding trials with surgery only or mixed (surgery or surgery plus
247 radiotherapy) locoregional treatment) showed similar results than the main analysis.

248 A majority of trials in this meta-analysis proposed induction chemotherapy. Despite a moderate effect on
249 survival³, induction therapy is sometimes advocated to reduce the risk of distant metastasis and to
250 reduce the tumor volume before surgery⁵. In our population of patients included in surgical trials,
251 induction therapy showed no significant benefit on overall survival or event-free survival. There was no
252 benefit on locoregional or distant failure. Effect was not significantly different for trials that proposed
253 only one cycle of chemotherapy or that allowed non-responding patients to have early surgery.
254 However, no trials proposed taxane in addition to PF, a strategy that proved significant benefit⁴⁵ over
255 induction PF. Except for a recent trial⁴⁶, trials comparing taxane + PF to PF alone did not include surgery
256 as LRT^{47,48} and could not be included in our meta-analysis. Finally, we could not study the benefit of

257 induction chemotherapy on organ preservation as trials included in this meta-analysis were not designed
258 to study organ preservation strategies.

259 An unexpected interaction between treatment effect and patients' characteristics was found for sex. This
260 differed from the overall MACH-NC analysis. In the MACH-NC analysis interaction was found only with
261 age (chemotherapy effect was poorer for patients older than 70 years old). This may result from
262 differences in patients' characteristics: patients treated by surgery are younger; only 387 (7.7%) of our
263 patients were older than 70 years and thus were analyzed in the ≥ 60 years old group. As the surgical
264 subgroup only represent 28.6% (5 000/17 483) of the MACH-NC population, 23.4% (2 696/11 542) of
265 observed deaths, and 14.3% of the patients included in concomitant trials (1 327/9 305), this interaction
266 might have been diluted in the overall analysis (eTable 1). This interaction was consistent for OS in
267 univariate and multivariate analyses. Results were similar for event-free survival. The study of the
268 heterogeneity of the interaction (eFigure5) and of the hazard ratios of treatment effect by sex (eTable7)
269 showed the consistency of the interaction throughout all trials; the leave-one-out analysis (eFigure6)
270 showed the robustness of the results. The effect of chemotherapy on the different type of failure in men
271 and women showed no significant difference on locoregional and distant failure. Men treated with
272 chemotherapy had a significantly higher incidence of death without failure. Interpretation of this
273 outcome was made difficult because of missing information on the exact cause of death. A lower rate of
274 comorbidities and of mortality not related to cancer in women than men may explain the observed
275 results. Despite the improvement over time of tumor control in HNSCC, survival increased moderately.
276 Authors pointed out that patients face many competing risks of death (toxicity, comorbidities, or second
277 malignancies)⁴⁹. In a recent communication, Park and al found that women with HNSCC died less from
278 other causes than from their tumors compared to men⁵⁰. Sex effect on toxicity and efficacy of systemic
279 treatment are debated, but often considered as understudied⁵¹. The prognostic value of sex has long
280 been discussed in HNSCC⁵²⁻⁵⁵; most of the time the better survival of women was linked to lower stage

281 tumors or better performance status. In a study evaluating multiple cancers and sex-specific survival,
282 Cook and al found better adjusted survival for women in flour of mouth and laryngeal cancer⁵⁶. Similar
283 results were observed in the controls arms (i.e. without chemotherapy) of the whole MACH-NC
284 database⁵⁷. The study of interaction between chemotherapy effect and sex is often difficult because of
285 the few women included in clinical trials. Only large trials or meta-analyses have sufficient power to
286 investigate such interaction and explore the predictive value of sex. As the exploration of sex differences
287 in medicine are actually promoted⁵⁸, future HNSCC trials should plan to stratify accrual on sex and to
288 study differences in efficacy and toxicity according to patients' sex.

289 Lack of power and risk of false positive are the main limitations of this study. Our population is a
290 subgroup of the MACH-NC patients treated with chemotherapy, but still allows an exhaustive synthesis
291 of most surgical trials available. Negative results such as the non-significant interaction between age and
292 chemotherapy effect, between early death and chemotherapy timing or non-significant effect of
293 chemotherapy on distant failure could be related to the lack of power. On the other hand, the
294 unexpected interaction with sex could be a false positive, but we found consistent results in favor of such
295 effect in exploratory analyses. Some trials included are old, patients were accrued between 1974 and
296 2000, and our results may not represent contemporary treatment strategies. Among the trials eligible for
297 the next update of MACH-NC, we have identified 2 concomitant trials^{59,60} and one induction trial⁴⁶ (476
298 patients) with surgical LRT, and sensitivity analysis adding these 3 more recent trials showed similar
299 results (data not shown). Another limitation was missing data. Some data were partially missing, such as
300 performance status, other were totally missing, such as HPV status, tobacco and alcohol consumption,
301 pathological characteristics, compliance to chemotherapy, or patients' comorbidity. This may be a
302 confounding factor in our analysis. However, all patients were included in randomized trials with
303 homogeneous inclusion and exclusion criteria and had limited comorbidities as surgery was possible,
304 minimizing differences between compared groups.

305 To conclude, this analysis confirmed the benefit of chemotherapy in addition to surgical LRT, however
306 benefit in OS was modest and may be limited to the use of platin, concomitant timing and/or to females.
307 The place of induction therapy has yet to be determined as it did not improved survival for patients
308 treated with induction chemotherapy followed by surgery. Our results suggested that women benefited
309 more from chemotherapy than men. Interaction between sex and chemotherapy should be further
310 investigated to confirm our results. As the benefit of chemotherapy in HNSCC is now widely
311 acknowledged, fewer trials compare chemotherapy in addition to LRT versus LRT only. Future analyses of
312 chemotherapy effect in HNSCC will require IPD network meta-analysis to provide high-level evaluation of
313 available treatments.

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321 and take responsibility for the integrity of the data and the accuracy of data analysis.

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503 **Figure legends**

504 **Figure 1: Hazard ratio of death with loco-regional treatment plus chemotherapy versus locoregional**
505 **treatment alone.**

506 This analysis was performed using a fixed-effect model. Heterogeneity is discussed in eTable 6 and in the
507 beginning of Discussion section. The broken line and center of the black diamond correspond to overall
508 pooled hazard ratio (HR) and the horizontal tip of the diamond is the 95% confidence interval (95%CI).
509 The center of the black square corresponds to the HR of trials. The area of the square and the variance of
510 (O-E) are proportional to the number of deaths in each trial. Trials are ordered chronologically (oldest at
511 the top of figure). CT = Chemotherapy, LRT = Loco-regional treatment; O-E = observed minus expected, I^2
512 = Higgins statistic for heterogeneity, No. = Number. In HNCP trial, the arm on induction CT and the one
513 on induction plus maintenance CT were pooled.

514 Trial group abbreviations:

515 AHNTG = Australian Head and neck Trial Group, BNH = B. Nanavati Hospital / Mumbai Group (India),
516 EORTC = European Organisation for Research and Treatment of Cancer, GETTEC = Groupe d'Etude des
517 Tumeurs de la Tête Et du Cou (France), GSTTC = Gruppo di Studio sui Tumori della Testa et del Collo
518 (Italy), HNCP = Head and Neck Contract Program (USA), HNU = Head and Neck UFT (Japan), , INT = US
519 INTer group trial, JHCFUS = Japanese HexyCarbanoyl 5-FluoroUracil Study, KKD = Kanto Koshinetsu
520 District (Japan), LOHNG = Ljubljana Oncology Head and Neck Group (Slovenia), RTOG = Radiation Therapy
521 Oncology Group (USA), SWOG = Southwest Oncology Group (USA), TMH = Tata Memorial Hospital
522 (India), UKHAN = United Kingdom Head And Neck (UKCCR head and Neck Collaborative Group, UK), Yale
523 = Yale University (USA).

524

525 **Figure 2: Overall survival curves by treatment arm for all trials and for trial subset defined by timing of**
526 **chemotherapy**

527 The slopes of the broken lines from year 7 to year 8 are based on the overall death rates in the seventh
528 and subsequent years. Absolute differences are given with their 95% confidence interval. LRT = Loco-
529 regional treatment, CT = Chemotherapy.

530 a) All trials; b) Adjuvant chemotherapy trials; c) Induction chemotherapy trials; d) Concomitant
531 chemotherapy trials.

532

533 **Figure 3: Hazard ratio of death with loco-regional treatment plus chemotherapy versus loco-regional**
534 **treatment alone by patient's characteristics.**

535 See Figure 1 Legend for more explanations.

536 p_inter: p-value of the test of interaction between individual characteristics and treatment effect.

537 p_trend: p-value of the test for trend; PS = performance status. 95%CI = 95% confidence interval

538 O-E = observed minus expected, No. = Number.

539 (a) 4 980 patients included in univariate Cox model for interaction.

540 (b) 4 829 patients included in univariate Cox model for interaction.

541 (c) Missing data in 19 trials (completely missing for BNH003 (124 patients), Cologne (97), Creteil 82 (122),
542 EORTC 24771 (231), EORTC 78-OCP (225), GETTECadj (286), JHCFUS (191), LOHNG97 (114), Pitie-74 (96),
543 TMHR-4 (135), Toulouse (90), Yale80po (78). Only 2811 patients included in univariate Cox model for
544 interaction (GSTTC86po and SWOG8006 had to be excluded because none of their patients had no
545 patients included in the PS=0 category)

546 (d) Only 2825 patients included in univariate Cox model for interaction because all trials had not included
547 patients in all 4 categories of interest (GETTECneo2, BNH003, Cologne, Creteil-82, EORTC24771,
548 EORTC24844, EORTC78-OCP, GSTTC86po, HNCP, KKD-86, Pitie-74, TMHR-4)

549 (e) Information on stage was not available for 2 trials (Pitie74 (96) and TMHR-4 (135)). Only 4 405
550 patients included in univariate Cox model for interaction (BNH003, GSTTC86po and LOHNG97 were
551 excluded because of the absence of stage I or II patients);

552

553 **Figure 4: Overall survival curves by treatment arm for all trials according to sex.**

554 On the right: men overall survival according to treatment. On the left: female overall survival according
555 to treatment arm. The slopes of the broken lines from year 7 to year 8 are based on the overall death
556 rates in the seventh and subsequent years. Absolute differences are given with 95% confidence interval.
557 LRT = Loco-regional treatment, CT = Chemotherapy.

558

559 **Figure 5: Cumulative incidence by treatment arm for each type of event (for overall analysis and for**
560 **each timing of chemotherapy).**

561 Given p values correspond to the comparisons of cumulative incidence between treated and non-treated
562 patients (stratified Fine and Gray test). The top left figure represents overall analysis.
563 CT = Chemotherapy; LRT = Locoregional treatment

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565

Figure 1: Hazard ratio of death with loco-regional treatment plus chemotherapy versus loco-regional treatment alone.

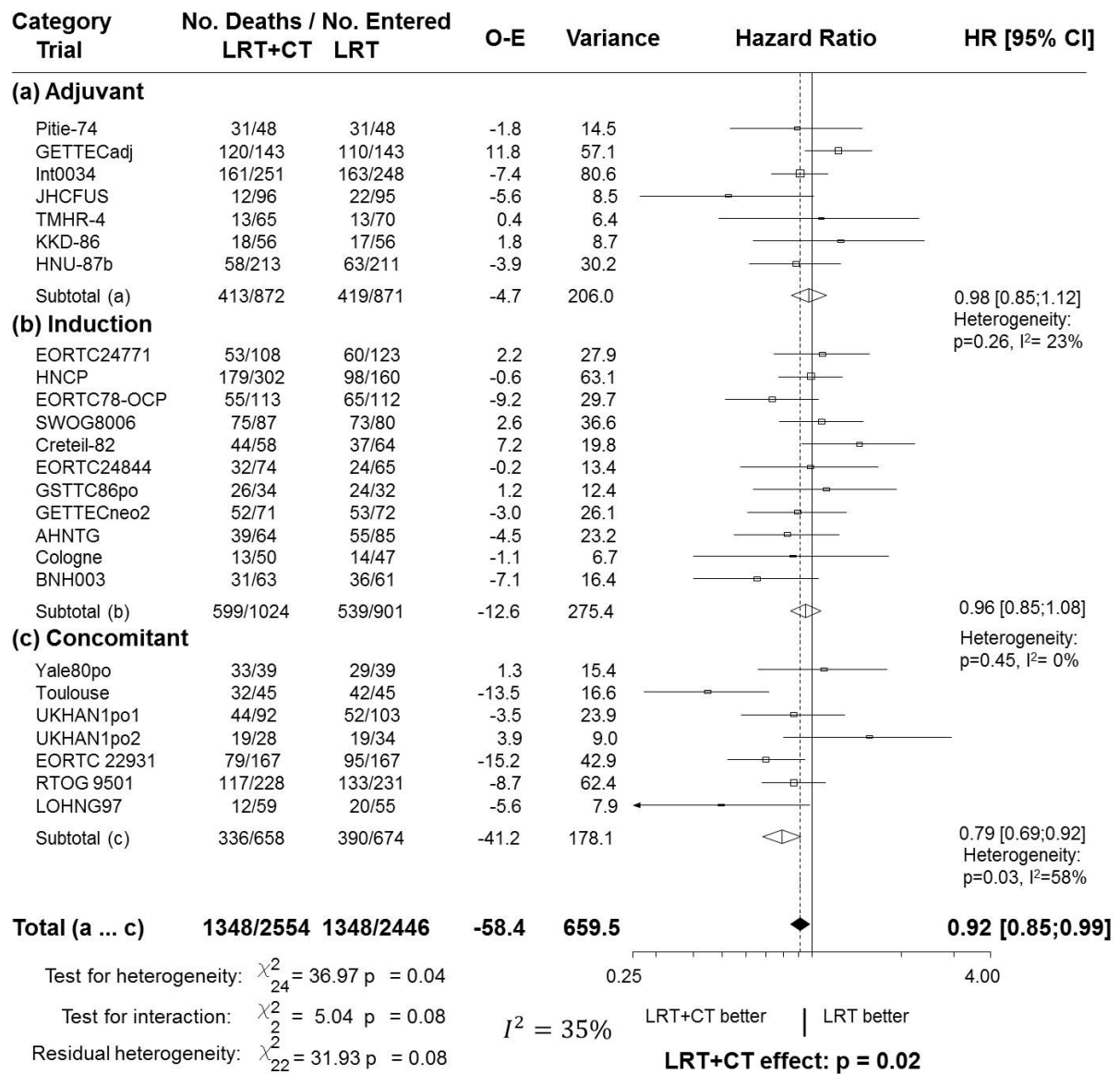


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Figure 2: Overall survival curves by treatment arm for all trials and for trial subset defined by timing of chemotherapy

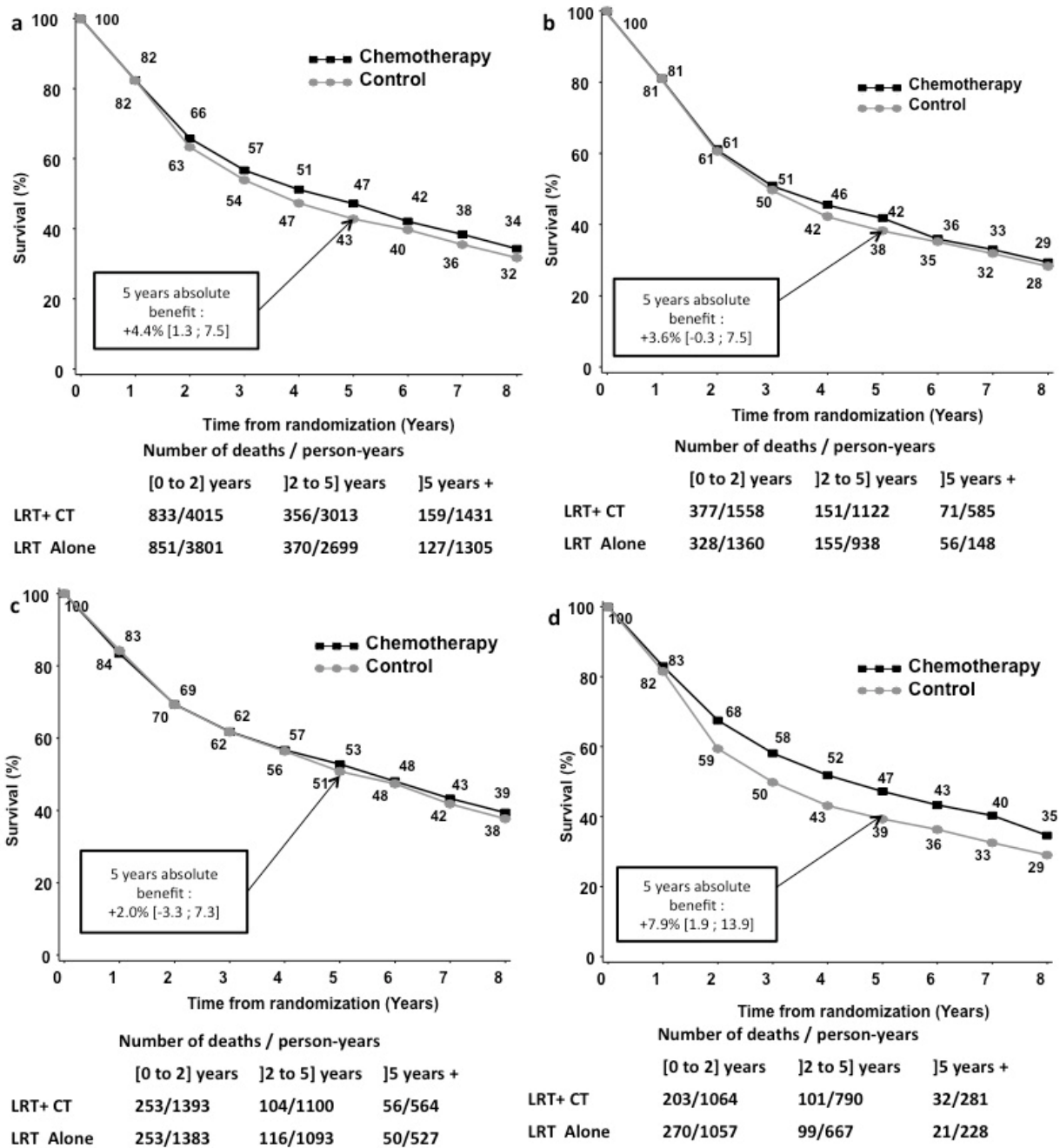


Figure 2: Overall survival curves by treatment arm for all trials and for trial subset defined by timing of chemotherapy

The slopes of the broken lines from year 7 to year 8 are based on the overall death rates in the seventh and subsequent years. Absolute differences are given with their 95% confidence interval. LRT = Locoregional treatment, CT = Chemotherapy.

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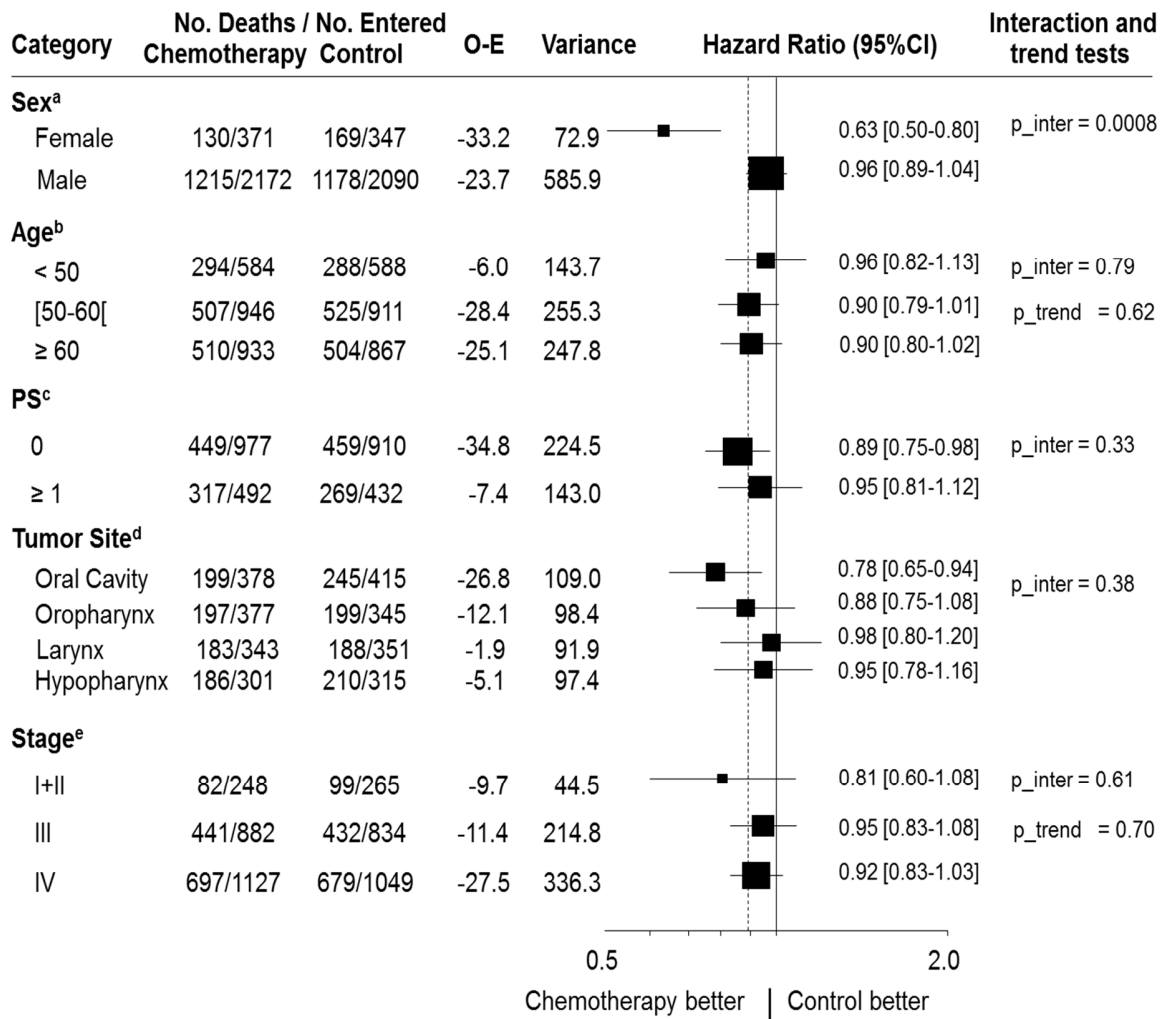


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Figure 4: Overall survival curves by treatment arm for all trials according to sex.

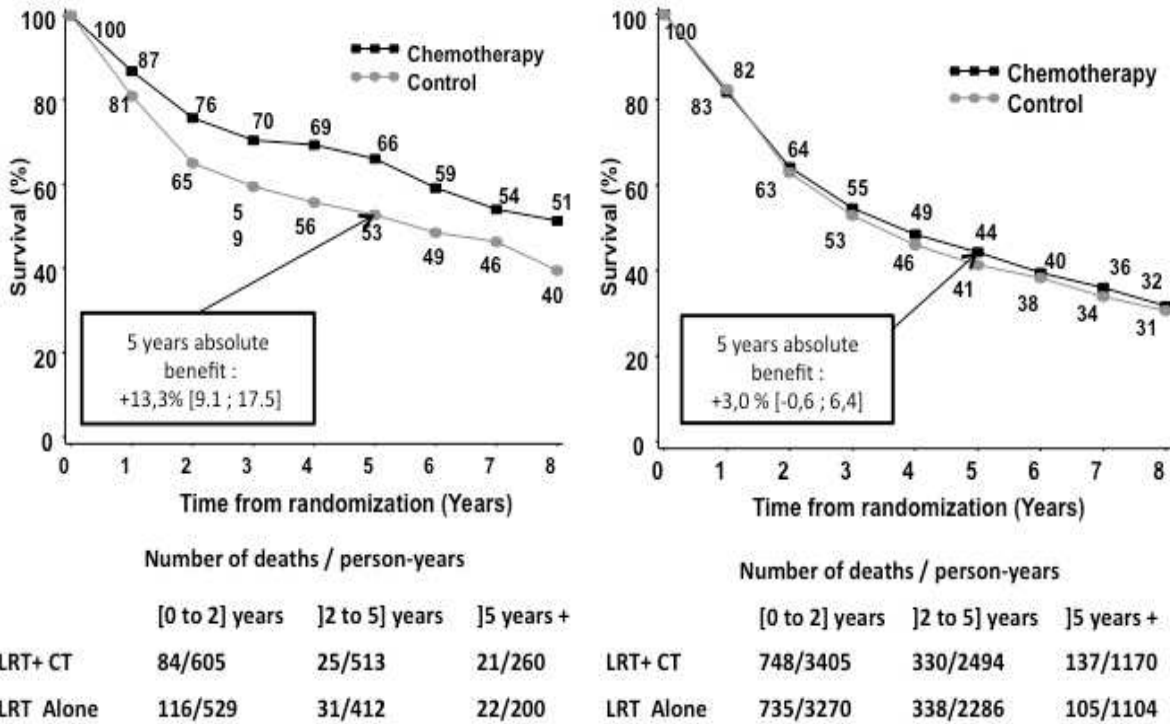


Figure 4: Overall survival curves by treatment arm for all trials according to sex.

On the right: men overall survival according to treatment. On the left: female overall survival according to treatment arm. The slopes of the broken lines from year 7 to year 8 are based on the overall death rates in the seventh and subsequent years. Absolute differences are given with 95% confidence interval. LRT = Loco-regional treatment, CT = Chemotherapy.

Figure 5: Cumulative incidence by treatment arm for each type of event (for overall analysis and for each timing of chemotherapy).

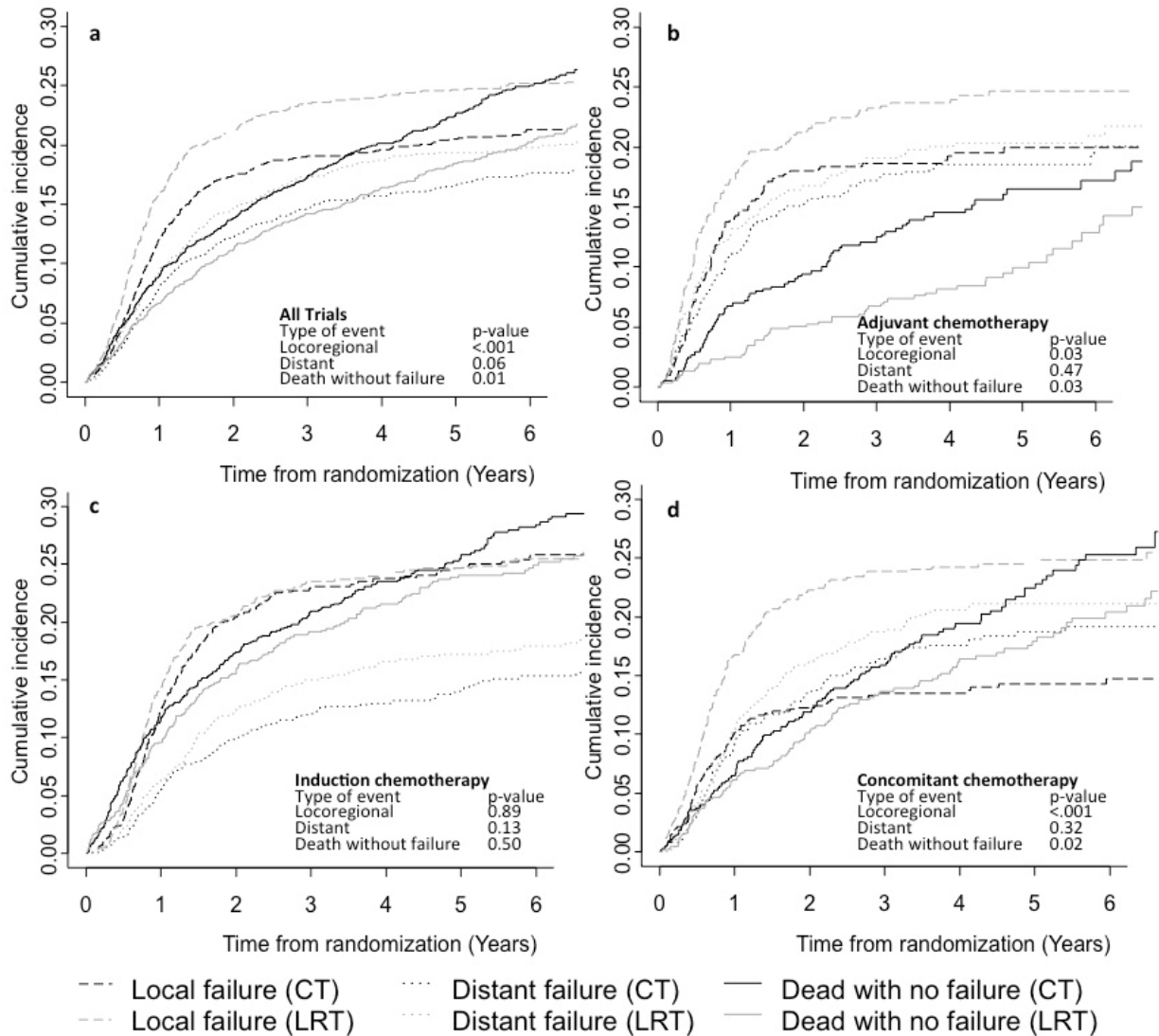


Figure 5: Cumulative incidence by treatment arm for each type of event (for overall analysis and for each timing of chemotherapy).

Given p-values correspond to the comparisons of cumulative incidence between treated and non-treated patients (stratified Fine and Gray test). a) All trials; b) Adjuvant chemotherapy trials; c) Induction chemotherapy trials; d) Concomitant chemotherapy trials. CT = Chemotherapy; LRT = Locoregional treatment