Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial

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Summary

Background The relative efficacy of the addition of induction chemotherapy to chemoradiotherapy compared with chemoradiotherapy alone for patients with head and neck cancer is unclear. The PARADIGM study is a multicentre open-label phase 3 study comparing the use of docetaxel, cisplatin, and fluorouracil (TPF) induction chemotherapy followed by concurrent chemoradiotherapy with cisplatin-based concurrent chemoradiotherapy alone in patients with locally advanced head and neck cancer.

Methods Adult patients with previously untreated, non-metastatic, newly diagnosed head and neck cancer were eligible. Patients were eligible if their tumour was either unresectable or of low surgical curability on the basis of advanced tumour stage (3 or 4) or regional-node stage (2 or 3, except T1N2), or if they were a candidate for organ preservation. Patients were randomly assigned (in a 1:1 ratio) to receive either induction chemotherapy with three cycles of TPF followed by concurrent chemoradiotherapy with either docetaxel or carboplatin or concurrent chemoradiotherapy alone with two cycles of bolus cisplatin. A computer-generated randomisation schedule using minimisation was prepared and the treatment assignment was done centrally at one of the study sites. Patients, study staff, and investigators were not masked to group assignment. Stratification factors were WHO performance status, primary disease site, and stage. The primary endpoint was overall survival. Analysis was by intention to treat. Patient accrual was terminated in December, 2008, because of slow enrolment. The trial is registered with ClinicalTrials.gov, number NCT00095875.

Findings Between Aug 24, 2004, and Dec 29, 2008, we enrolled 145 patients across 16 sites. After a median follow-up of 49 months (IQR 39–63), 41 patients had died—20 in the induction chemotherapy followed by chemoradiotherapy group and 21 in the chemoradiotherapy alone group. 3-year overall survival was 73% (95% CI 60–82) in the induction therapy followed by chemoradiotherapy group and 78% (66–86) in the chemoradiotherapy alone group (hazard ratio 1·09, 95% CI 0·59–2·03; p=0·77). More patients had febrile neutropenia in the induction chemotherapy followed by chemoradiotherapy group (16 patients) than in the chemoradiotherapy alone group (one patient).

Interpretation Although survival results were good in both groups there was no difference noted between those patients treated with induction chemotherapy followed by chemoradiotherapy and those who received chemoradiotherapy alone. We cannot rule out the possibility of a difference in survival going undetected due to early termination of the trial. Clinicians should still use their best judgment, based on the available data, in the decision of how to best treat patients. The addition of induction chemotherapy remains an appropriate approach for advanced disease with high risk for local or distant failure.

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Introduction

The treatment of patients with locally advanced head and neck cancer continues to improve. There are in essence two different, non-surgical approaches available to treat these patients: concurrent chemoradiotherapy and induction chemotherapy followed by concurrent chemoradiotherapy.[1] Concurrent chemoradiotherapy has emerged as a preferred treatment approach on the basis of various studies establishing the efficacy of cisplatin-based chemoradiotherapy.[2–4] The standard approach has been to give cisplatin at 100 mg/m² every 3 weeks during radiation therapy. The benefit of concurrent chemoradiotherapy was also shown in a meta-analysis of head and neck cancer.[5,6] No clear benefit exists in the addition of biological therapy to chemoradiotherapy, although the role of cetuximab and radiotherapy is being examined more closely in selected patient populations.[7,8] Induction chemotherapy has been added to chemoradiotherapy to try to decrease the likelihood of emergence of distant metastasis, improve local regional control, and support organ preservation. A regimen of docetaxel, cisplatin, and fluorouracil (TPF) has emerged as the standard induction

chemotherapy regimen on the basis of phase 3 studies establishing its superiority over cisplatin and fluorouracil (PF) induction chemotherapy.[9,10] This benefit of TPF has been recorded in patients with both resectable and unresectable disease. It has also been observed in patients with laryngeal cancer treated for organ preservation.[11] However, whether the addition of induction chemotherapy to chemoradiotherapy improves efficacy compared with chemoradiotherapy alone is unclear.

The PARADIGM study is an open-label, randomised, phase 3 study comparing two different treatments: induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in patients with locally advanced, previously untreated, head and neck cancer.

Methods

Participants

In this open-label, randomised, phase 3 trial, patients with measurable, previously untreated, non-metastatic, histologically proven stage III or IV squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were eligible if the tumour was deemed to be either unresectable (because of tumour fixation, involvement of the nasopharynx, or fixed lymph nodes) or of low surgical curability on the basis of advanced tumour stage (3 or 4) or regional-node stage (2 or 3, except T1N2), or if the patient was a candidate for organ preservation. Patients had to be at least 18 years of age with a WHO performance status of 0 or 1 and adequate bone marrow, liver, and renal function measured with blood tests. Exclusion criteria were any previous chemotherapy or radiotherapy, a cancer diagnosis within the previous 5 years, severe weight loss (>25% of bodyweight) in the preceding 2 months, symptomatic altered hearing or peripheral neuropathy greater than grade 1 by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, and any other serious illnesses or medical disorders such as chronic obstructive pulmonary disease requiring admission to hospital within the previous 12 months or unstable cardiac disease.

Patients were enrolled across 14 hospitals: 13 in the USA and one in Europe. Disease was staged according to the criteria of the American Joint Committee on Cancer. All patients provided written informed consent, and every study centre was required to have approval from its institutional review board before randomisation.

Randomisation and masking

Patients were randomly assigned (in a 1:1 ratio) to receive either induction chemotherapy (three cycles of TPF) followed by concurrent chemoradiotherapy (group A) or definitive concurrent chemoradiotherapy (group B). A computer-generated randomisation schedule using minimisation was prepared, and the treatment assignment was done centrally at one of the study sites. Stratification factors included WHO performance status (0 or 1), primary disease site (oropharynx or other), and stage (T1, T2, T3 and N0, T3 and N1, or other). Patients, study staff, and investigators were not masked to treatment group assignment.

Procedures

For induction chemotherapy, TPF was given as docetaxel 75 mg/m² intravenously on day 1; cisplatin 100 mg/m² intravenously on day 1, and fluorouracil 1000 mg/m² on days 1–4 as continuous infusion. Cycles were repeated every 3 weeks for three cycles. Primary prophylaxis with G-CSF was allowed. To take full advantage of the benefits of a sequential treatment plan and optimise the outcome for patients in group A, after the three cycles of induction chemotherapy, patients were stratified by response to a more or less intensive chemoradiotherapy. Patients who responded poorly to induction chemotherapy (on the bases of: any progressive disease; if the patient did not complete all three cycles of induction chemotherapy; clinical partial response in neck adenopathy and greater than 2 cm neck adenopathy on CT/MRI; grossly positive primary site tumour [no exam under anaesthesia and biopsy necessary]; and clinical partial response or stable disease in the primary site and positive biopsy) were assigned to receive concurrent chemoradiotherapy with weekly docetaxel at 20 mg/m² for 4 weeks (group A1).

All other patients were deemed to have responded favourably and were assigned to group A2, in which chemoradiotherapy was given with weekly carboplatin area under the curve (AUC) 1·5 for 7 weeks as per the

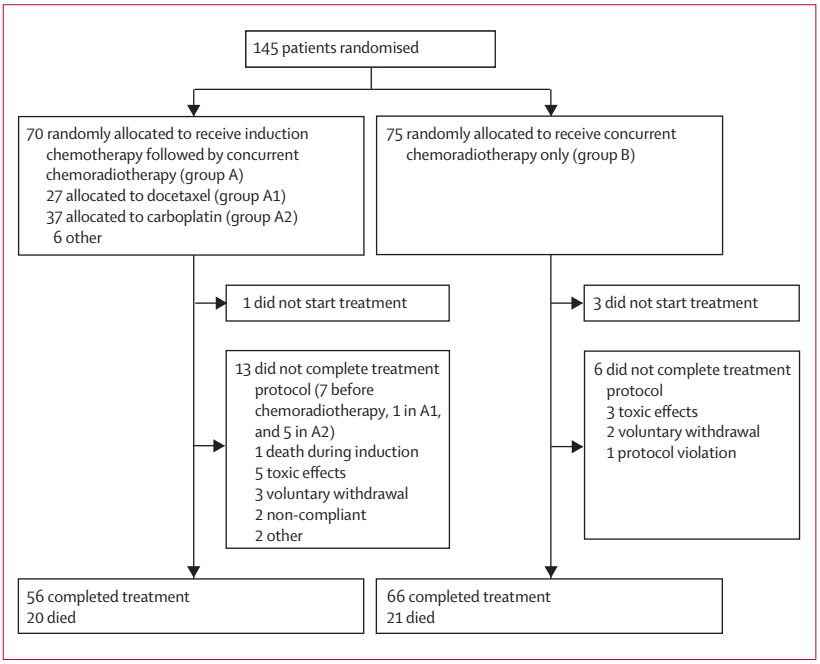

Figure 1: **Trial profile**

TAX 324 study.[9] The chemoradiotherapy group (group B) consisted of two doses of cisplatin at 100 mg/m² given on days 1 and 22 of radiation therapy. Elective neck dissections were done if necessary after the completion of chemoradiotherapy.

For groups A1 (induction chemotherapy followed by chemoradiotherapy with docetaxel) and B (chemoradiotherapy with cisplatin only): radiotherapy was given as accelerated concomitant boost over 6 weeks. The total dose was 72 Gy, in 1·8/1·5 Gy fractions. For group A2 (induction chemotherapy followed by chemoradiotherapy with carboplatin), radiotherapy was given once daily over 7 weeks. Total dose was 70 Gy, in 2·0 Gy fractions. In both cases, radiotherapy was given 5 days a week (ie, excluding weekends). For patients who received induction chemotherapy, chemoradiotherapy after TPF phase of chemotherapy started within a minimum interval of 3 weeks and no later than 8 weeks after the start of the last cycle of TPF (day 22 to 56 after the start of the last cycle). This design was the same as in the TAX 324 study and is meant to allow patients to recover from the third cycle of TPF. Chemoradiotherapy was expected to start as soon as possible after induction allowing for counts recovery and radiation planning to occur.

We defined disease failure as any local, regional, or distant failure. Adverse events were assessed according to the National Cancer Institute CTCAE (version 3.0). We only recorded the following adverse events: mucositis, febrile neutropenia, pain, xerostomia, feeding tube placement, and neuropathy, which we deemed pertinent to the comparison of regimens in this setting. We defined a serious adverse event or reaction as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient admission to hospital or prolongation of existing hospital stay, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect. Human papillomavirus (HPV) status was not obtained in this trial.

Statistical analysis

The primary endpoint of this study was overall survival. Secondary endpoints were progression-free survival and toxic effects. This trial was designed to detect a 40% reduction in the hazard rate and assumed a 3-year survival of 55% for group B (chemoradiotherapy only). Assuming 100 patients were enrolled per year for 3 years, followed for an additional 2 years, and allowing for one interim analysis before the final analysis at 125 deaths, 300 eligible patients (150 per group) provided 80% power to detect an improvement in 3-year survival from 55% with chemoradiotherapy alone to 70% with induction chemotherapy followed by chemoradiotherapy using a one-sided 0·025 level log-rank test to compare groups. These survival assumptions were made on the basis of available data[2–4] in the published literature when the study was originally designed. Allowing for 10% ineligibility rate, the plan was to accrue a total of 330 patients.

	Induction chemotherapy followed by concurrent chemoradiotherapy (n=70)	Concurrent chemoradiotherapy only (n=75)
Ethnic origin		
White	64 (91%)	63 (84%)
Other	6 (9%)	12 (16%)
Age (years)		
Minimum–maximum	35–72	36–74
Median (IQR)	55 (50–61)	54 (48–60)
Sex		
Female	6 (9%)	12 (16%)
Male	64 (91%)	63 (84%)
WHO performance status		
0	47 (67%)	50 (67%)
1	23 (33%)	25 (33%)
T stage		
T1	4 (6%)	6 (8%)
T2	28 (40%)	21 (28%)
T3	22 (31%)	29 (39%)
T4	16 (23%)	19 (25%)
N stage		
N0	7 (10%)	10 (13%)
N1	6 (9%)	4 (5%)
N2	50 (71%)	55 (73%)
N3	7 (10%)	6 (8%)
Stage		
III	10 (14%)	11 (15%)
IV	60 (86%)	64 (85%)
Primary disease site		
Hypopharynx	8 (11%)	7 (9%)
Larynx	10 (14%)	14 (19%)
Oral cavity	13 (19%)	13 (17%)
Oropharynx	39 (56%)	41 (55%)

Data are number of patients (%) unless otherwise indicated.

Table 1: **Patient characteristics**

	Induction chemotherapy followed by concurrent chemoradiotherapy (n=70)	Concurrent chemoradiotherapy only (n=75)
Any disease failure	17 (24%)	19 (25%)
Local or regional only	9 (13%)	6 (8%)
Distant only	3 (4%)	3 (4%)
Both	2 (3%)	5 (7%)
Unknown	3 (4%)	5 (7%)
Total local or regional	11 (16%)	11 (15%)
Total distant	5 (7%)	8 (11%)

Data are number of patients (%).

Table 2: **Pattern of disease failure (36 cancer failures)**

	HR (95% CI)*	p value	3-year rates (95% CI)	
			Induction chemotherapy followed by concurrent chemoradiotherapy	Concurrent chemoradiotherapy only
Progression-free survival				
Number of events			23	22
Progression-free survival	1·07 (0·59–1·92)	0·82	67% (54–76)	69% (56–79)
Oropharynx	1·79 (0·71–4·56)	0·22	67% (49–80)	83% (66–92)
Non-oropharynx	0·72 (0·33–1·58)	0·42	66% (45–80)	55% (35–70)
Number of deaths				
Number of events			20	21
Overall survival	1·09 (0·59–2·03)	0·77	73% (60–82)	78% (66–86)
Oropharynx	1·40 (0·55–3·55)	0·47	73% (55–84)	83% (67–92)
Non-oropharynx	0·86 (0·36–1·99)	0·72	73% (52–85)	72% (52–84)

HR=hazard ratio. *Based on log-rank test for group A *vs* group B.

Table 3: **Summary of outcomes**

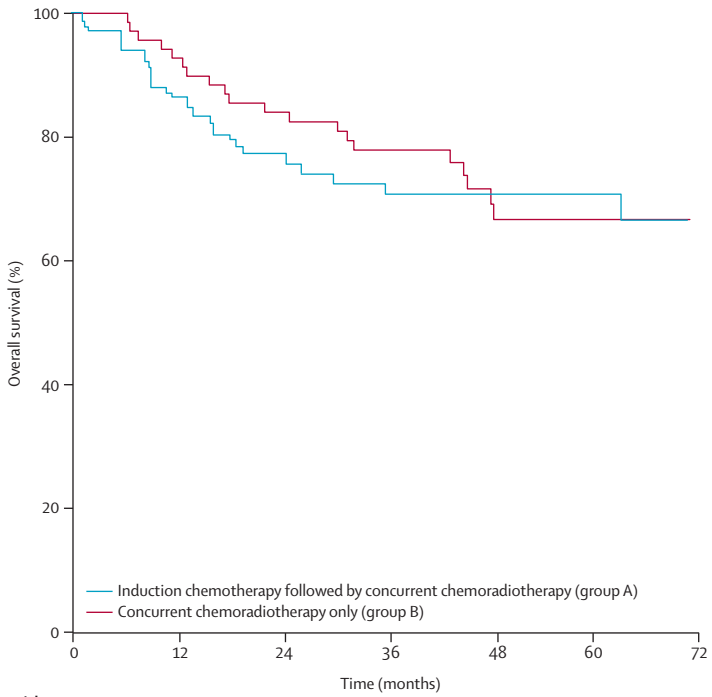

Figure 2: **Kaplan-Meier estimates of overall survival**

We defined overall survival as the time from date of randomisation to death from any cause. Patients alive at the time of current analysis were censored at the date last known to be alive. Progression-free survival was defined as the time from date of randomisation to disease progression or death from any cause without progression whichever occurred first; otherwise, patients were censored at the date last known to be free of progression. Analyses of outcome were done by intention to treat among eligible patients. We used the Kaplan-Meier method to estimate overall survival and progression-free survival distributions and the log-rank test was used to assess differences in these distributions with respect to treatment. All analyses were done with SAS version 9.2. The trial is registered with ClinicalTrials.gov, number NCT00095875.

Role of funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Aug 24, 2004, to Dec 29, 2008, we enrolled 145 patients across 16 sites. The study was halted because of slow accrual. 70 patients were assigned to receive induction chemotherapy followed by chemoradiotherapy (group A) and 75 patients assigned to receive chemoradiotherapy only (group B; figure 1). The primary analysis cutoff was March 30, 2012. Patient characteristics were well balanced between groups (table 1). Patients were relatively young with a median age of 54 years, mostly men, and white. All patients entered had a WHO performance status of 0–1 as mandated per protocol. Most patients had stage IV disease (124 [86%] of 145 patients). The main primary site was oropharynx (80 [55%] of 145 patients). 13 patients (9%) had N3 disease. 35 (24%) patients had T4 disease.

Median follow-up was 49 months (IQR 39–63). 36 disease failures occurred: 17 (24%) of 70 patients who received induction chemotherapy and 19 (25%) of 75 patients who did not receive induction chemotherapy (table 2). We noted no clinically significant differences between the two groups with respect to number or site of recurrence (table 2). 41 patients died (20 patients who received induction chemotherapy and 21 patients who received chemoradiotherapy alone). 31 patients had disease progression as cause of death (14 patients who received induction chemotherapy and 17 patients who received chemoradiotherapy alone) and 10 patients died because of other causes (six patients who received induction chemotherapy and four patients who received chemoradiotherapy alone). 3-year overall survival did not differ between the study groups (table 3, figure 2). Progression-free survival did not differ between groups (table 3 and figure 3).

We noted non-significant trends in favour of the addition of induction chemotherapy for patients with non-oropharyngeal cancers in terms of progression-free survival, and in favour of chemoradiotherapy alone for patients with oropharyngeal cancers in terms of both progression-free survival and overall survival (table 3). We also undertook an analysis to assess outcome in patients with N2b/N2c and N3, and we noted no advantage for the addition of induction chemotherapy to

chemoradiotherapy compared with chemoradiotherapy alone in that group (data not shown).

Within the induction chemotherapy followed by chemoradiotherapy group, both overall survival and progression-free survival were higher in the group of patients receiving weekly carboplatin (group A2) than in the group of patients receiving weekly docetaxel (group A1): 3-year progression-free survival was 44% (95% CI 24–62) for group A1 and 86% (70–94) for group A2 and overall survival was 52% (95% CI 31–69) for group A1 and 92% (76–97) for group A2.

With regard to toxic effects, we noted no differences between the groups in mucositis scores, pain scores, xerostomia, neuropathy, or feeding tube dependency (table 4). Toxic effects did not differ between groups A1 and A2 either (data not shown). Febrile neutropenia differed between groups. In the induction chemotherapy followed by chemoradiotherapy group, ten patients had febrile neutropenia of grade 3 and six patients of grade 4 compared with one patient who had grade 4 febrile neutropenia in the chemoradiotherapy only group. 52 serious adverse events were reported in the induction chemotherapy followed by chemoradiotherapy group and 22 in the chemoradiotherapy only group.

Radiation breaks were not common on the trial. 11 patients (six in the induction chemotherapy with chemoradiotherapy group and five in the chemoradiotherapy alone group) had a radiation break of 5 days or more. No treatment-related deaths occurred on this study.

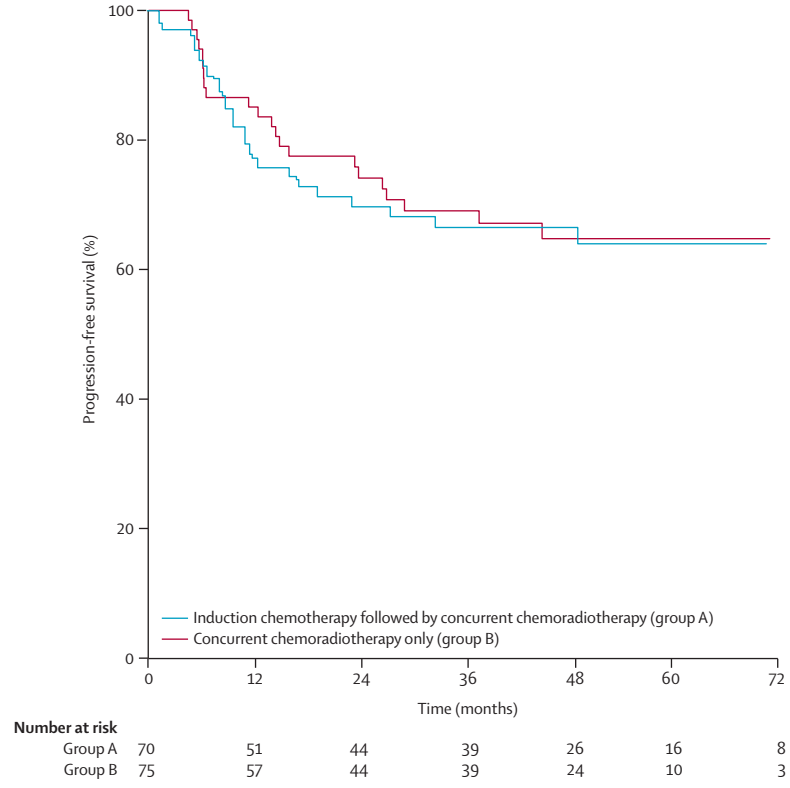

Figure 3: **Kaplan-Meier estimates of progression-free survival**

	Induction chemotherapy followed by concurrent chemoradiotherapy (n=70)	Concurrent chemoradiotherapy only (n=75)
Mucositis		
Grade 1–2	29 (41%)	44 (59%)
Grade 3–4	33 (47%)	12 (16%)
Febrile neutropenia		
Grade 3–4	16 (23%)	1 (1%)
Pain		
Grade 1–2	41 (59%)	35 (47%)
Grade 3–4	2 (3%)	9 (12%)
Xerostomia		
Grade 1–2	42 (60%)	46 (61%)
Grade 3–4	5 (7%)	5 (7%)
Neuropathy		
Grade 1–2	22 (31%)	18 (24%)
Grade 3–4	0	2 (3%)
PEG tube placed	55 (79%)	64 (85%)

Data are number of patients with events (%). PEG=percutaneous endoscopic gastrostomy.

Table 4: **Toxic effects (frequencies shown)**

Discussion

Our findings show no overall survival advantage with induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy only. The trial closed prematurely in 2008 with insufficient accrual and power to see the predicted difference because survival was better than expected in both groups. A clinically important survival difference could have gone undetected at a significant level with this sample size.

The TAX 323[10] and TAX 324[9] studies, published in 2007, investigated the important question of identifying the optimal induction chemotherapy regimen to use in head and neck cancer. These two studies and later the GORTEC laryngeal study[11] showed that TPF was significantly better than PF for survival, local control, and organ preservation. These studies defined a new standard of care for induction chemotherapy in the USA and Europe, and also led to regulatory approval of TPF for patients with resectable and unresectable disease. However, these studies did not answer the fundamental question about the relative efficacy of adding induction chemotherapy to chemoradiotherapy compared with chemoradiotherapy alone, the current standard of care.

Concurrent chemoradiotherapy has evolved over the years and level one evidence exists to support the use of bolus cisplatin at 100 mg/m² in patients with laryngeal cancer for organ preservation,[2] in patients with high-risk disease receiving postoperative therapy,[12,13] and in patients with unresectable disease.[4] A meta-analysis also confirmed the overall survival benefit of concurrent

chemoradiotherapy, which appeared to be more pronounced than that achieved with induction chemotherapy.[5,6] Because of the large difference between the two concepts of therapy and the questions as to the relative efficacy of induction or sequential therapy compared with chemoradiotherapy, it has become essential to compare these two paradigms—ie, concurrent chemoradiotherapy and sequential therapy (panel). An early comparison was provided in the RTOG 91-11 larynx preservation trial.[14] In this trial, both the concurrent and induction groups proved to be better than radiotherapy alone in terms of laryngectomy-free survival, the primary endpoint of the study.[14] Larynx preservation was best achieved with concurrent chemoradiotherapy, whereas overall survival at 5 years favoured the induction chemotherapy group, although the difference was not statistically significant.[14]

The addition of induction chemotherapy to concurrent chemoradiotherapy was examined by a randomised phase 2 Italian study.[15] Two groups were compared: TPF followed by chemoradiotherapy versus chemoradiotherapy alone. During chemoradiotherapy, PF was used as the chemotherapy backbone in both groups. The primary endpoint was complete radiographic response. The study showed the sequential chemoradiotherapy group to be better than the concurrent group, with higher complete response rates: 21·2% for concurrent versus 50% for sequential.[15] These findings led to the Italian phase 3 study comparing the two treatments. This study has completed accrual and is waiting for sufficient follow-up before reporting.

A Spanish group also did a large phase 3 study comparing induction chemotherapy regimens.[16] Two induction chemotherapy regimens were studied: TPF followed by chemoradiotherapy and PF followed by chemoradiotherapy. This study was designed before it was known that induction TPF was superior to PF. The study looked at time to treatment failure as a primary endpoint, and showed a benefit in the induction groups: 5 months of time to treatment failure in the concurrent chemoradiotherapy group versus 12·5 months in the induction groups,[16] on the basis of a per-protocol analysis. No intention-to-treat analysis was presented. Final results of this study have not been published yet.

The preliminary results of the DeCIDE trial have also been presented.[17] In this phase 3 study, TPF followed by chemoradiotherapy was compared with chemoradiotherapy alone. Only patients with N2 and N3 stages were included in this study. This study was also terminated early because of slow accrual and, as in our trial, did not show a survival improvement with the addition of induction chemotherapy,[17] although induction chemotherapy appeared to reduce the cumulative incidence of distant metastasis compared with chemoradiotherapy alone.

Our study did not complete accrual and was closed early. Many factors contributed to the early closure: competing trials in the USA at that time, patient preference, and strong physician preferences within the oncology community. Additionally, pre-existing preference in regard to induction chemotherapy with chemoradiotherapy for more advanced disease might have created a selection bias in the USA against the risk of randomisation to chemoradiotherapy alone. Similarly, the complexity of the trial might also have made it difficult for patients presented with the prospect of randomisation. The two treatment options are quite distinct, with the regimen containing induction chemotherapy being substantially longer than the other.

The study design took into consideration multiple factors; treatment for patients deemed to have responded favourably to induction chemotherapy was the same as for the experimental group in TAX 324,[9] in which patients were given weekly carboplatin and radiation. We designed the regimen for those who were deemed to have responsed poorly to induction therapy on the basis

***Panel:* Research in context**

Systematic review

We reviewed papers in major journals and assessed reported trials over three decades; we reviewed and participated in meta-analyses done by the MACH group, which reviewed all randomised trials in the field.[5] The evidence supports the superiority of a TPF (docetaxel, cisplatin, and fluorouracil) induction approach in advanced disease on the basis of the superior comparison of TPF with PF (cisplatin and fluorouracil) and the effectiveness of PF in randomised clinical trials. No evidence exists by direct comparison indicating the superiority of concurrent chemoradiotherapy over a TPF induction or sequential approach, which was the main reason to perform this trial. All comparative well powered studies, including the recently published Intergroup 91–11 larynx preservation trial,[14] support this notion. Meta-analysis shows differences between trials and treatment programmes wherein trial selection, inclusion, or exclusion criteria in chemoradiotherapy trials compared with induction trials might have systematically biased survival in the meta-analysis comparison.

Interpretation

Our findings did not show that adding induction chemotherapy to chemoradiotherapy was better than concurrent chemoradiotherapy alone in locally advanced head and neck cancer. Both groups in this study did exceedingly well in a patient population that is composed primarily of stage IV disease. Clinicians should still use their best judgment, based on the available data, in the decision of how to best treat patients. The addition of induction chemotherapy remains an appropriate approach for advanced disease with high risk for local or distant failure. HPV should be addressed as a significant prognostic factor and therapy adjusted based on this risk assessment.

of our previous experience with the poor responders to TPF, which used a regimen of weekly docetaxel with accelerated radiotherapy.[18] The chemoradiotherapy regimen chosen was the same as in the experimental group in RTOG 0129. We now know that this group is as effective as three doses of cisplatin and standard daily radiation.[19]

The survival of patients in the chemoradiotherapy only group in this study was unexpectedly good. When the study was designed in 2002–03, 55% survival at 3 years was a reasonable choice for the power calculation in the chemoradiotherapy alone group based on the available scientific literature at the time. Similar assumptions were made for the DeCIDE trial.[17] Since then, advances in our understanding of the epidemiology and subsequent changes in prognosis and survival of patients with head and neck cancer have been striking. The reason for this is multifactorial. Oropharyngeal cancer that is related to HPV infection is a clear factor[20,21] and, as we now know, these patients have a favourable prognosis and have survival rates well into the 70–90% range.[19,22,23] HPV-related oropharynx cancer affects young patients who generally are very healthy and have excellent tolerance to therapy. These patients are typically non-smokers and often have primary disease in the tonsils or base of tongue. Cystic nodal disease is often associated with this entity. HPV status was not obtained in our study and smoking status was not uniformly recorded but it is fair to assume that many of the patients with oropharynx cancer enrolled in this trial have HPV-related oropharynx cancer and thus are destined to do very well with any treatment. It is also possible that the treatment itself has improved with better radiation delivery and supportive care. This last argument is more difficult to prove but obvious to many clinicians in the clinic.

The absence of HPV data is a weakness in our study. The trial was initiated in 2004; before that and over the next 5 years HPV determination for oropharyngeal cancer was both unreliable and expensive. Moreover, the effect of HPV on survival was not fully appreciated and thus HPV testing was not included or considered in the plan. Because of the early termination and the restricted funding, retrospective collection of the data and materials was not feasible.

Unplanned subgroup analysis suggested that concurrent chemoradiotherapy alone was superior to a regimen containing induction chemotherapy in oropharyngeal cancers, whereas the advantage of induction chemotherapy may be demonstrable in non-oropharyngeal sites (non-significant differences). It is quite conceivable that, because of the epidemic of HPV-related oropharynx cancer we are currently witnessing, it will be very hard to see a survival advantage with any modality in studies that include HPV-related oropharyngeal cancer or fail to stratify for this entity. In this context, PARADIGM with its original design including both HPV-related and unrelated cancers would very probably still be a negative trial, had it completed its original accrual target. Moving forward, it is imperative to study HPV-related cancers as a separate entity or at least stratify for HPV status. Currently ongoing studies in the USA and Europe are focusing on such topics, asking therapeutic questions specific to HPV-related or unrelated cancers. We have effectively entered a new era in head and neck cancer wherein, for the first time, we have an important prognostic marker such that, stage for stage, significant differences in outcome and different biology exist with different potential therapeutic pathways.

An interesting observation can be made in the separation between those patients who received intensified chemoradiotherapy after induction and those who received standard chemoradiotherapy after induction in relation to progression-free and overall survival advantage. Even though not significant, the trends recorded are clinically significant and the criteria used to enter either group seem to be important to determine patients likely to respond to additional induction chemotherapy with chemoradiotherapy. The intensification of therapy for the non-responders did not seem to overcome biologically aggressive tumours. This poor trend observed in non-responders or poor responders to induction chemotherapy deserves further investigation.

The question of whether the addition of induction chemotherapy to concurrent chemoradiotherapy improved survival over concurrent chemoradiotherapy alone remains unfortunately unanswered and it might not be answered soon. Both treatment modalities are effective in the treatment of head and neck cancer. A cost-benefit and quality-of-life analysis might prove beneficial in addressing the true value of induction chemotherapy while integrating stratification on HPV status in this disease.

Contributors

RH, MP, and RT conceived and designed the study. RH, MP, RT, DA, JC, JJB, and FK recruited and treated the patients. RH, FK, JJB, DA, JC, SR, GR, JL, and SL obtained the clinical data. RH, MP, SL, JL, NS, AO, and GR analysed and interpreted the data. AO did the statistical analyses. RH, MP, and GR wrote the final report. All authors reviewed and approved the final draft of the report.

Conflicts of interest

RH received research grants and is a consultant to Alder Biopharmaceuticals, Boehringer Ingelheim, Astra Zeneca, and Exilixis. MP is a consultant to Eisai, Cel-Sci, and Oncolytics, and is a stock holder of Promedior. NS was employed by Sanofi-Aventis at the time of the study and owns stock for Sanofi-Aventis. All other authors declare that they have no conflicts of interest.

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