Avant
Avant Mutual Group Limited
ABN 58 123 154 898

28 November 2016

Please reply to Sydney Office
Our Ref: HT:1601034_01
Your Ref:

Private and confidential
Jenny Whight
Senior Officer
Parliament House
Macquarie Street
Sydney NSW 2000

Dear Ms Whight

Off-protocol Prescribing of Chemotherapy in NSW - Post Hearing Responses

Dr John Grygiel

There are two points we would like to emphasise:

(1) Section 122 Inquiry – Inconsistency of approach

Whilst there was an emphasis on a rigid criterion for complying with accepted eviQ guidelines in the treatment of St Vincent's patients with carboplatin, it appears that in regard to capecitabine there was more acceptance to deviate from the guidelines when it became apparent that many oncologists were prescribing significantly less than the prescribed eviQ dose. We note that the report into treatment in Western NSW LHD states at paragraph 30 that "*due to the capecitabine-associated toxicity, a large proportion of capecitabine could be expected to be within 25% of this commonly used starting point,…".* Paragraph 48 notes "*as explained in paragraph 37, the inquiry's clinical experts indicated that, due to associated-toxicity, many medical oncologists would commence capecitabine treatment at a dose 20-25% lower than the dose used in the defining clinical trial*" and also 20-25% lower than what is recommended in the eviQ guidelines.

(2) Radiosensitisation

As Dr Haines indicated low dose chemotherapy is radiosensitisation. It is to "*change the structure and function of cells without severely damaging them making them more susceptible to the lethal effect of the primary radiation treatment*" (Haines). We agree that the combination of chemotherapy and radiotherapy is far more toxic than radiotherapy alone. We also recognise that there is no formula to calculate the dose for maximal radio sensitisation.

Dr Haines indicates that "*recent data reveals that it is the completion of the scheduled radiotherapy within the defined protocol time and not the completion of the protocol chemotherapy that determines the outcome for the patient*".

In response to your email dated 1 November 2016, we **attach** the following documents:

1. Corrected transcript, 1 November 2016,
2. Answer to question taken on notice, please find **attached**, two emails dated 22 February 2016,
3. Answer to supplementary question, please find **attached**, the answer dated 28 November 2016,
4. Opening Statement of Dr John Grygiel,
5. Submission No 64, Dr Jodi Lynch, 22 October 2016.
6. Articles:
    a. P, Kaur et al, *Concurrent Low Dose Carboplatin with Radiotherapy Versus Radiotherapy Alone in Management of Locally Advanced Head and Neck Cancer Patients* (2012).
    b. I, Haines, *St Vincent's Scandal: What's the protocol for chemotherapy and are low doses less effective?* The Conversation (2016).
    c. I, Haines, *Chemotherapy: More is often not better* (MJA 10th October 2016).
    d. J, Pignon et al, *Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients* (2009).
    e. J, Pignon et al, *Chemotherapy added to Locoregional Treatment for head and Neck Squamous-cell Carcinoma: Three meta-analyses of updated individual data* (2000).
    f. E.B, Douple et al, *Carboplatin as a Potentiator of Radiation Therapy* (1985). The transcript made reference to a Douple article in1987, the correct year of the article is 1985, and the corrected transcript includes this amendment.

Yours faithfully
Avant Law Pty Ltd

Helen Turnbull, Special Counsel Professional Conduct
Sydney

Helen Turnbull

From: Helen Turnbull
Sent: Monday, 28 November 2016 12:50 PM
To: Helen Turnbull
Subject: emails relating to the 31st August 2015

From: Brett Gardiner
Sent: Monday, 22 February 2016 8:28 PM
To: Stephen Blanks
Cc: johngrygiel Brett Gardiner
Subject: Re: Grygiel statement

Stephen

I have just read the attached statement and will escalate to the CEO for formal response to the main body of the statement. Notwithstanding, I do wish to clarify the section where I am mentioned.

On 31 August 2015, a meeting was held between Dr Grygiel, Dr Gallagher, and Dr Gardiner concerning the allegation of 'under-dosing' of patients with Carboplatin. At this meeting, Dr Grygiel's reasons for prescribing the dose of carboplatin which were at variation to the EviQ protocol were discussed. The reasons outlined by Dr Grygiel included the toxicity of Carboplatin on patients and various evidence as to the effectiveness of various dosage regimes. The meeting was part of the internal process review and no criticisms were made of Dr Grygiel. It was noted at the meeting that recurrences in the small number of patients identified were outside the primary radiotherapy treatment zone, and were considered to be probably not related to the clinical dosing decision made by Dr Grygiel.

I will refer on tonight for the organisation to formally respond to the proposed statement.

Regards

Brett

Dr Brett Gardiner

Director Clinical Governance & Chief Medical Officer

St Vincent's Health Network Sydney

Address: St Vincent's Hospital (Executive Unit Level 3, de Lacy Building)

390 Victoria Street, Darlinghurst NSW 2010 | **e:**

On 22 Feb 2016, at 6:09 PM, Stephen Blanks wrote:

Dear Sirs

I act for Dr John Grygiel.

Dr Grygiel proposes to issue the attached statement tomorrow morning at 9.30am.

Should you have any questions or concerns about the statement, please contact me urgently.

Regards

Stephen

<image001.jpg>

Connect with Stephen <image002.png> | **Follow SBA Lawyers**
<image003.png> | **Follow Stephen** <image004.png>

SELECT COMMITTEE ON OFF-PROTOCOL PRESCRIBING OF CHEMOTHERAPY IN NSW

Inquiry into off-protocol prescribing of chemotherapy in New South Wales

Hearing: **Sydney, Tuesday 1 November 2016**

For Dr John Grygiel, Medical oncologist

1. Could you please provide the date that Dr Gallagher phoned you to suggest you take early retirement?

Dr Grygiel's Response

I received an email from Richard Gallagher dated 27 November 2015 (attached) whilst I believe he was attending a meeting in London. The email stated "*Have you considered what we discussed last Sunday? I arrive back on Sunday. If I don't hear from you I will contact on Monday.*"

I believed that the discussion which is referred to as "*discussed last Sunday*" occurred on 22 November 2015 whilst Dr Gallagher was waiting to board his flight to London. This was the conversation I was referring to in the transcript, page 12.

28/11/2016

From: Richard Gallagher
Date: 27 November 2015 at 5:35:52 pm AEDT
To: John Grygiel
Subject: Med Onc

John,

Have you considered what we discussed last Sunday?
I arrive back on Sunday.
If I don't hear from you I will contact on Monday.

Richard

Submission
No 64

INQUIRY INTO OFF-PROTOCOL PRESCRIBING OF CHEMOTHERAPY IN NSW

Name: Dr Jodi Lynch

Date received: 22 October 2016

Legislative Council

Select Committee on off-protocol prescribing of chemotherapy in NSW

Inquiry into off-protocol prescribing of chemotherapy in NSW

Submission by Dr Jodi Lynch* FRACP, Medical Oncologist, St George Hospital and Sutherland Hospital, Senior Staff Specialist

Introduction

This inquiry concerns off-protocol prescribing of chemotherapy. Before making assumptions, it is first necessary to address whether this is inherently bad and should be avoided, which seems to be assumed in the nature of the inquiry.

The use of trial protocols has been extremely useful in advancing the treatment of cancer, but in practice there are many situations where patients do not fit into evidence based regimens. Although protocols are useful, their use still requires clinical judgement, just as a road map is only a guide to a journey and does not give you all the information you need to travel.

The development of clinical practice "guidelines" in NSW has been the result of a collaborative effort of many oncologists but none of us believe that they were intended to represent a rigid formula to which prescribing for individual patients requires 100% adherence. There can be catastrophic consequences of rigid prescribing by the application of guidelines advocating for strict dosing protocols. Limiting prescribing removes the expert from the equation and I would argue that this would be overwhelmingly detrimental.

Firstly "protocols" that are used in NSW Health EVIQ clearly state that they are only guidelines, and there are many factors that must be taken into account by the treating physician. I attach a copy of the dosing notes from the EVIQ website that set this out in more detail (Table 1). We aim for personalised medicine and know there is an inherent delay from protocol development to implementation.

Table 1 – eviQ Guidelines from https://www.eviq.org.au/Copyright.aspx

Secondly, medicine and oncology in particular is very dynamic with new scientific discoveries all of the time. Bringing new discoveries from the bench to the bedside helps patients enormously. Sometimes there is limited evidence and it may take years for an idea to be proven. Without oncologists interpreting the data, there is no cutting edge treatment. For example, Carboplatin and Cisplatin in BRCA associated Breast Cancer. For years patients with BRCA associated ovarian cancer were thought to be more sensitive to platinum agents and extrapolation of this to BRCA patients who experience triple negative breast cancer has only been realised in recent years. As the numbers are low, the data is few and protocols are rare or non-existent. Does this mean we do not offer this treatment? I would argue it would be senseless to ignore.

Most oncologists in NSW operate in a peer review environment and at both formal and informal meetings oncologists discuss these issues at length. Most oncologists in Australia are members of the Medical Oncology Group of Australia (MOGA) and or the Clinical Oncological Society of Australia (COSA) and these associations provide forums for appropriate prescribing. The tumour stream interests allow for vigorous discussion and debate, and like anything there will always be controversy and disagreement.

It is also important for the Committee to appreciate that chemotherapy is given for two reasons; curative intent and palliation.

When giving chemotherapy for palliative reasons we seek to relieve pain and provide a better quality of life. Dose reduction may be relevant in these circumstances. Chemotherapy is inherently toxic, and the protocols are based on trials. Trials are usually conducted with suitable patients who are otherwise well and uncomplicated; there are strict criteria for inclusion and exclusion. We often have patients with other illnesses, and full dose chemotherapy may not be the best course of treatment in all cases. Indeed, Lyman has published data from patients being treated with curative intent in Breast Cancer. In a national practice pattern study, less than 50% of patients received 85% dose intensity. This is telling of the toxicity in the standard population that led clinicians to reduce the dose in normal day to day practices.

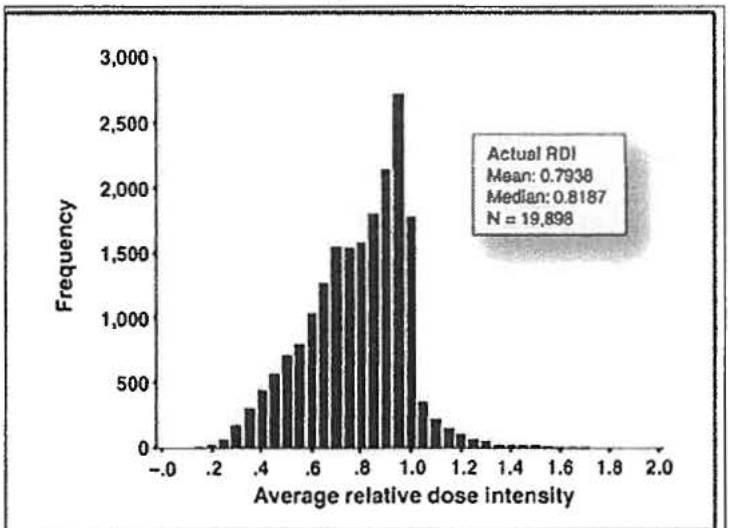


Figure 6: RDI Data From National Practice Pattern Study— Distribution of relative dose intensity observed among nearly 20,000 women receiving adjuvant chemotherapy for early-stage breast cancer in a US national practice pattern study. More than half of women received less that 85% of the standard dose intensity for their adjuvant regimen. RDI = relative dose intensity. Adapted, with permission, from Lyman.[4]

Table 2 – Lyman GH, Dale DC, Crawford J: Incidents and predictors of low dose intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 21:4524-4531, 2003

There are often very sound reasons to use different starting doses. For example, Cabazitaxel was established in the 2nd line castrate-resistant prostate cancer setting in the TROPIC study using a dose of 25mg per metre square in a study where the majority of patients received GCSF (a colony stimulating factor that decreases risk of major infection). GCSF is not available on the PBS in the palliative setting in Australia. Without GCSF, the risk of neutropaenia is unacceptably high in some older patients. There were treatment-associated deaths reported in the pivotal study which used GCSF, so dose-modifcation at least initially is necessary in Australia with consideration to titrating the dose up as tolerated.

I will now address the specific terms of reference.

a) **The efficacy of electronic prescribing systems, and their capacity to stop or limit off-protocol prescribing of chemotherapy.**

St George and Sutherland Hospitals have an electronic medical record system called ARIA. While ARIA has a module for electronic prescribing, it is not available to clinicians at St George and Sutherland.

The system currently in place requires clinicians to clearly outline the treatment plan with the protocol and doses, discuss the dose schedule, and outline concurrent therapy. It also outlines the tests included in monitoring the patient and the plan for follow up. Chemotherapy is written on paper charts.

More recently it has been mandated to put the EVIQ protocol number on this treatment plan form. If there is no EVIQ protocol, then clinicians are encouraged to include an evidence based protocol such as a journal article, to support cytotoxic drugs being ordered. As far as I'm aware this is kept by the pharmacy and not included in the patient notes. More recently a chemotherapy write up meeting has been established which is supervised by senior clinicians and attended by registrars. This meeting is part of a peer-review process and an aid in teaching.

EVIQ is an online service of the Cancer Institute of NSW. It seeks to standardise treatment for patients so equitable care can be provided anywhere in the country. Before EVIQ, clinicians at each centre would have chemotherapy protocol books. Protocol would be included by the clinician if they thought they were best practice. These protocols were discussed at Journal Clubs or hospital meetings. Now, clinicians super-specialise and treat a specific tumour stream eg Breast, Gynaecological, Lung, Genitourinary, Brain etc. EVIQ annually hold protocol review committees for each tumour stream and the committee decides what stays on the protocol list and what is introduced. This has been enormously helpful as the rigorous debates by super-specialised oncologists lifts the standards and allow Australia to have one of the leading survival rates of cancer in the world.

Many members of staff at St George and Sutherland are members of the EVIQ protocols committee (I am a member of the Breast committee) and we encourage our registrars to attend these annual meetings where chemotherapy protocols are proposed and reviewed. The discussion at these

meetings is often around the evidence that is presented and discussed. Many of the experienced clinicians at this meeting discuss the toxicity they have seen with the standard doses that are recommended. Sometimes a protocol is left as is stated in the trial but full dosage is rarely used.

There is much data in the literature about appropriate prescribing, either under-dosing or over-dosing. The long term survival data is conflicting and controversial. The Clinical Oncological Society of Australia has produced a document for safe prescribing of chemotherapy in 2008 and I attach this document for your information (Appendix 1). Within this there is also a guideline about what suggested information is to be provided to the patients.

Recommendation: At St George and Sutherland Hospitals there is no electronic prescribing system and so this cannot be used to stop or limit off-protocol prescribing of chemotherapy. Electronic prescribing has many checks that may improve safety and should be a priority for NSW Health. Off EVIQ protocol prescribing of chemotherapy should be available but it needs to be justified and clearly documented. This allows new treatment into the clinic and prevents undue toxicity that may lead to excess costs to NSW health. Peer review is important and participation in these processes should be mandatory.

b) **The value of a potential new patient information sheet on dose adjustment for patients and caregivers information.**

Clinicians currently discuss with patients when a dose adjustment is being made and why. For example, in patients with abnormal liver function tests there is often a dose adjustment made, and this is often outlined in the original protocol. Dose adjustments are also made for myelosuppression, neurotoxicity, life threatening sepsis, and other grade 3-4 toxicities from previous cycles of treatment.

Recommendation: There is no value in providing a patient information sheet on dose adjustment as it would cause undue anxiety. Dose adjustments depend on the aim of treatment. If our aim of treatment is palliation, then dosing is adjusted for the quality of life of the patient. If our aim of treatment is cure, then clinicians favour standard dosing unless there are clear indices such as organ impairment, which necessitate dose reductions as mandated in the protocol.

c) **The process and systems around informed consent for all medical interventions, including chemotherapy.**

Informed consent is an essential component of prescribing chemotherapy. Information being discussed regarding side effects and toxicities is always discussed verbally and written information is provided at the same time. This has been standardised in recent years with the use of EVIQ protocols. If non-standard prescribing is used, then patients can be informed by using slides or protocols and papers presented at meetings, which have not yet been discussed at the EVIQ protocol meetings at the Cancer Institute.

Sometimes patient diaries are recommended and information on supportive medications, such as anti-nausea medication and anti-diarrheals are provided. Informed consent at St George and

Sutherland is very thorough. Major toxicities are always discussed and as cytotoxics are dangerous drugs, the possibility that the drugs could cause life threatening illness and death is discussed. This discussion also talks about the aim of treatment and personally I check to see that patients have understood what I have said, so that they don't ignore problems that may be quite serious. Their consent is documented in the notes.

Before administration of chemotherapy, the nursing staff repeats this process of educating the patients about potential toxicities. There is a rigorous 2 tier process at St George and Sutherland to ensure understanding, and this is often repeated and reinforced at subsequent consultations.

d) **The capacity of the NSW Health system to have all notifiable cancer patients in New South Wales overseen by a Multidisciplinary Cancer Care Team and if this may prevent off-protocol prescribing.**

I am the chair of the multidisciplinary team ("MDT") breast meeting at St George Public, Sutherland and St George Private Hospitals. We have a combined meeting every second Wednesday. All patients with newly diagnosed breast cancer are discussed and some patients who have progressed with advanced disease or who have unusual problems are also discussed. The purpose of an MDT is to decide overall management of each case to ensure each patient receives optimal care. Members of the team include surgeons, pathologists, radiation and medical oncologists, radiologists, nurses, geneticists, psychologists and trial coordinators.

Recommendations for treatment are a "pathway level" for example if radiation is thought to be necessary, then radiation is recommended or if chemotherapy is necessary, then chemotherapy is recommended and likewise with surgery. But we do not discuss which protocol of chemotherapy or what dose of radiation should be given or tell the surgeon which operative technique to use. These details are left to the clinician who will see the patient.

There is no way the multidisciplinary cancer care team can supervise or prevent off-protocol prescribing. As these meetings comprise of a diversity of professionals as well as medical oncologists, they are not an appropriate forum to discuss the particular type of chemotherapy or the doses used. Members other than medical oncologists have no expertise in dosing and drugs.

Recommendation: There is no capacity for the multidisciplinary team to oversee off-protocol prescribing.

e) **St Vincent's Hospital capability to comply with relevant NSW Health Policy Directives and Guidelines, particularly Open Disclosure Policy (PD2014_028) and Incident Management Policy (PD2014_004).**

I cannot comment on this, as I am not a clinician at St Vincent's Hospital.

f) **The NSW Health Code of Conduct and specific programmes within NSW Health and St Vincent's Hospital, in relation to staff raising concerns about the practice of clinicians, and other breaches of the Code of Conduct.**

The NSW core health values are collaboration, openness, respect and empowerment. Staff are recommended to promote a positive work environment, demonstrate honesty and integrity, act professionally and ethically, including maintaining and enhancing professional standard skills and keeping up to date with best practice, using official resources lawfully, efficiently and as authorised, and maintaining security and confidentiality, as well as maintaining professional relationships with patients.

Employees are encouraged to report any issues or incidents of clinical care that raises concern about standards of practice. Staff are encouraged to report to their manager. Additionally there are staff forums to discuss cases that are controversial including morbidity and mortality meetings; these are performed regularly within each department and generally within the divisions of medicine, surgery etc. to ensure that peer-review is an important part of practice.

All grievances are recommended to be discussed with the individual staff member with a manager proportionate to the issues raised, respecting the rights and perspective of the individual. This part of the code of ethics can be interpreted in many ways and with regards to the current inquiry to prescription of chemotherapy in NSW. At St George and Sutherland while the rights of the staff raising concern have been respected, the rights of the clinician have not sufficiently been taken into account. The dignity of a well-respected local clinician, Dr Kiran Phadke, has been removed. Subsequent vilification by the media of my colleague, Dr Phadke, could have been avoided and better processes could have been put in place.

Discussion of the cases at a department or Cancer Services level with scientific evidence presented is a far more effective way in providing guidance to clinicians which leads to best practice. Supervision and further education may remediate this situation and this is more respectful than suspension. It allows communication and reconciliation rather than persecution. When our junior colleagues underperform, they are performance managed. If a senior clinician's performance is thought to be unsatisfactory, the same methods should be applied.

Conclusion

Cancer treatment is complex and dynamic. For a clinician to avoid under-treating or over-treating a patient, scientific evidence and clinical judgment must be used. There is little level one evidence for a linear dose-cure relationship in many patients, such as those with early breast cancer. It is important that we don't simply rely on protocols that use a dose that will provide unacceptable toxicities. Protocols are often based on clinical trials on patients who are otherwise healthy with little comorbidities (ie other health issues). Many patients that are referred for clinical trials are rejected, as they do not fit the strict inclusion and exclusion criteria.

Patients that we see day to day are often sick and have multiple comorbidities, which must be taken into account. If we don't err on the side of caution, the implication to the health system may be worse with more admissions due to side effects that could have been prevented. Personalised care is ideal and it is important that oncologists are not mandated to follow outdated protocols or protocols that are flawed, rather than provide state of the art cancer treatment.

The oncologist's job is a balance between science and art. Protocols provide a solid foundation to practice that needs to be adapted from patient to patient according to the ethics of medicine; beneficence, non-maleficence, autonomy and justice. We must continue to advocate for "first do no harm".

The central conflict appears to be between the ability of other staff to question a medical oncologist with regards to choice of treatment and being able to collect information that can provide the checks and balances to ensure high quality care.

The key to ensuring better outcomes is collecting more data, in a well designed system that can give better feed back to clinicians on their choices of care. For example, so that comparisons could be made between different protocols for the same disease group. NSW Health has failed to provide clinicians with these tools. A more helpful inquiry would be one that investigates into the failure of implementing a unified patient record of treatment across hospitals. There are different systems in different hospitals, each implemented in a different manner, they do not talk to each other, and they are difficult (and different) to use.

The processes involving informed consent are rigorous and are documented. Multidisciplinary cancer care teams are not the appropriate vehicles to monitor chemotherapy prescribing as many members of the team are not trained in this regard.

Finally, the NSW Health Code of Conduct is a rigorous document and supports any staff member raising a concern about the practice of a clinician. However, the process to be followed whenever such a concern is raised is poorly outlined, subsequent dealings with the clinician concerned are haphazard, there is little proper process that is followed and the impact on the clinician can be devastating, regardless of the substance of the complaint.

* Dr Jodi Lynch FRACP is a Senior Medical Oncologist at St George and Sutherland Hospitals. Dr Lynch has a private practice at St George Private, and is also a co-joint lecturer at the University of New South Wales.

Comparative Study

Concurrent Low Dose Carboplatin with Radiotherapy Versus Radiotherapy alone in Management of Locally Advanced Head and Neck Cancer Patients

Paramjeet Kaur, *Assistant Professor,*
Department of Radiation Oncology, Regional Cancer Centre, PGIMS, Rohtak, Haryana, India.

Ashok Chauhan, *Senior Professor & Head Unit II,*
Department of Radiotherapy, PGIMS, Rohtak, Haryana.

Gajender Singh, *Assistant Professor,*
Department of Pathology, PGIMS, Rohtak, Haryana.

Abstract

A prospective study was performed to evaluate the efficacy and safety of concurrent chemotherapy with single agent low dose Carboplatin and radiotherapy on survival, functional and quality of life outcomes in locally advanced head and neck cancer patients. *Material and Methods :* Sixty inoperable, previously untreated locally advanced head and neck cancer patients were planned to be treated with radical radiotherapy 66 Gy with concurrent single agent chemotherapy with low dose Carboplatin 150 mg IV weekly up to 6.3 weeks (Group A) and conventional radical radiotherapy alone (Group B). *Results :* After completion of therapy in Group A complete response was observed in 19/30 (63%) patient and in control group B in 10/30 (33%).Grade II mucosal toxicities were observed in 40% of cases and 33 % of cases in study and control group respectively. *Conclusion :* Concomitant single agent chemo radiotherapy with low dose Carboplatin could be a better choice in advanced stage of Head and Neck carcinoma in terms of survival, acceptable toxicities together with enhanced response and quality of life.

Keywords

head and neck malignancies, concurrent chemotherapy, carboplatin, radio sensitizer

Introduction

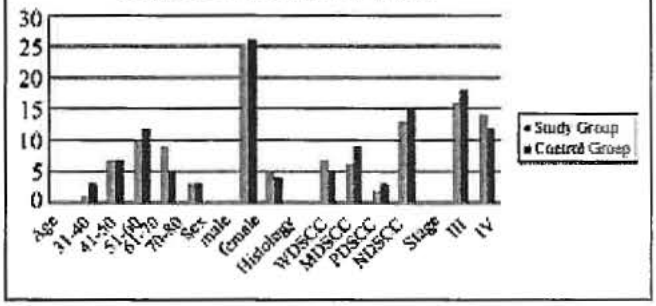
Cancer of the head and neck is the frequent malignant tumour in world[1]. Annually, ten million new cancer cases are reported worldwide, out of which half a million are cancers of head and neck[2,3]. In India incidence is more than 25% of all malignancy. Majority of cases 70%- 80% are locally advanced (Stage III- IV) at the time of diagnosis with lymph node involvement in 30 -35 % of patients[4].

Currently management in these cases comprised multimodality approach which aims at improved survival, local control, reduction of distant metastasis and above all preservation of organ function without jeopardizing the overall outcome. In addition to radiotherapy and surgery, concomitant chemo radiotherapy is designed to be third definitive treatment in locally advanced head and neck cancer[6, 7].

Superiority of combined radiotherapy and chemotherapy to RT alone has shown in most of the randomized clinical trials in these tumours. Metaanalysis of chemotherapy on head and neck cancer MACH-NCI demonstrated 12% reduction in the risk of death corresponding to an absolute improvement of 4% in 5-year survival with CT & RT[8]. In most of the trials combination chemotherapy used with

Address for correspondence: Dr Paramjeet Kaur, Assistant Professor, Department of Radiation Oncology, Regional Cancer Centre, 15/11J Medical campus, Rohtak, Haryana -124001, E-mail: dr_paramjit_ g @ yahoo. co. In

Fig. 1
Patients Characteristics



Response

After completion of treatment, patients who had no clinical evidence of disease either at the primary site or in the regional lymphnodes nor had any evidence if distal metastasis, were considered as 'complete remission'. Those who had > 50% decrease of the tumour size and regional lymph nodes were considered 'partial remission' (PR).

All patients were completed six months of follow up. As shown in **Table 1** & **2** 63.33% patients had no evidence of disease in the study group as compared to control group; 33% patients were disease free.

Table 1
Response after completion of treatment

No	Response	Group A		Group B	
		No	%	No	%
1.	CR	18	60	13	43.33
2.	PR	10	33.33	10	33.33
3.	NR	2	7	7	23.33
4.	PD	0	0	0	0

Table 2
Responses at the End of last follow up

No	Response	Group A		Group B	
		No	%	No	%
1.	NED	19	63.33	10	33.3
2.	Residual	8	27	15	50
3.	Recurrence	3	10	5	17

Toxicities

Acute toxicities were acceptable. More toxicity was observed in study group in comparison to control group. Toxicities were acceptable, neither interruption nor treatment prolongation were required in both groups. However, eight patients were required blood transfusion.

Table 3
Haematological toxicities in study group

Grade	Anaemia		Leucopenia		Platelets	
	No	%	No	%	No	%
0	5	17	19	63	21	70
I	13	43	8	27	6	23
II	8	27	2	7	2	7
III	3	10	1	3	1	3
IV	1	3	—	—	—	—

Table 4
Cutaneous toxicities during radiation therapy

Grade	Study Group		Control Group	
	No	%	No	%
I	18	60	22	73
II	10	33	8	27
III	2	7	—	—
IV	—	—	—	—

Table 5
Mucosal toxicities during treatment

Grade	Study group		Control group	
	No	%	No	%
1	8	27	18	60
2	12	40	10	33
3	10	33	2	7
4	—	—	—	—

Discussion

Cancer of the head and neck constitutes one of the commonest malignancies in India. Radiotherapy has been the main mode of treatment for head and neck cancer. But

chemotherapy concepts. *Semin Oncol.* **15**:70-85, 1988.

5. Stupp R., Weichselbum R. R., Vokes E. E. — Combined modality therapy of head and neck cancer. *Semin Oncol.* **21**:349-358, 1994.

6. Forastiere A. A. — Chemotherapy of head and neck cancer. In: Haskell C. M., Berek J. S., editors. Cancer treatment. Phildephia: WB Saunders Company. 733-740, 1995.

7. Wolf G. T., Lippman S. M., Laramore G. E., Hong W. K. — Neoplasms of head and neck . In: Holland J. F., Frei E., Bast R. C., Kuff D. W., Morton D. L., Weichselbaum R. R., editors. Cancer Medicine. Philadephia : lea and Febiger. 1211-1267, 1993.

8. Pigon J. P., Bourhis J., Domene *et al.* — Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma:Three meta-analysis of updated individual data. MACH-NC Colloboration Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet.* **355**:949-955, 2000.

9. Kurihara N., Kubota T., Hoshiya Y., *et al.* — Pharmacokinectics of cis-diamminedichloroplatinum (11) given as low dose and high dose infusions. *J Surg Oncol.* **62**:135-138, 1996.

10. Nagai N., Ogata H. — Quantitative relationship between pharmacokinectis of unchanged cisplatin and nephrotoxicity in rats. Importance of area under the concentration –time curve (AUC) as the major toxicodynamic determinant in vivo. *Cancer Chemother Pharmacol.* **40**:11-18, 1997.

11. Glick J. H., Tayolar S. G. N. — Integration of chemotherapy into a combined modality plan for head and neck cancer. A review. *Int J Radiat Oncol Biol Phys.* **4**: 354-358, 1981.

12. Gatenby R. A., Kessler H. B., Rosenblum J. S., Coia L. R., Moldofsky P. J., Hartz W. H., *et al.* — Oxygen distribution in squamous cell carcinoma metastasis and its relationship to outcome of radiation therapy. *Int J Radiat Oncol Biol Phys.* **14**:831-838, 1988.

13. Brizel D. M., Dodge R. K., Clough R. W., *et al.* — Oxygenation of head and neck cancers; changes during radiotherapy and impact on treatment outcome. *Radiother Oncol.* **53**:113-117, 1999.

14. Nordsmark M., Bentzen S. M., Rudat V., *et al.* — Prognositc value of tumour oxygenation in 397 head and neck tumours after primary radiation therapy. An International multicentre study. *Radiother Oncol.* **77**:18-24, 2005.

15. Hennequin C., Favaudon V. — Biological basis for chemo-radiotherapy interactions. *Eur. J. Cancer.* **38**:223-230, 2002.

16. Jeremic B., Shibamoto Y., Stanisvljevic B., Milojevic L., Milicic B., Nikolie N. — Radiation therapy alone or with concurrent low dose daily either Cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck. *Radio Ther Oncol.* **43**(1): 37-39, 1997.

17. Ausili Cefaro G., Marmiroli L., Nardone L., Salvi G. — Prolonged continuous infusion of carboplatin and comcomitant radiotherapy in advanced head and neck cancer. *Am Chin Oncol.* **18**(3):273-276, 1995.

18. Marmiroli L., Ausili C'efaro G., Nardone L., Fiorentino G., Genovesi D., Salvi G. — Combined radiochemotherpy for organ preservation in head and neck cancer. *Rays.* **22** (3): 425-440, 1997.

19. Glicksman A. S., Wanebo H. J., Slotman G. , Liu L., Landmann C., Clark J., Zhu T. C., Lohri A., Prdist R. —Concurrent platinum based chemotherapy and hyperfractionated radiotherapy with late intensification in advanced head and neck cancer. *Int J Radiat Oncol Biol Phys.* 1:39(3):721-729, Oct 1997.

THE CONVERSATION
Academic rigour, journalistic flair

Some cancer patients at St Vincent's hospital were treated with off-protocol doses of a chemotherapy drug. Alastair Gilfillan/Flickr, CC BY

The New South Wales government this week released the final report of its investigation into chemotherapy "underdosing" of patients with locally advanced head and neck cancer in a Sydney hospital.

The report was commissioned after the ABC reported in February that up to 70 cancer patients at St Vincent's Hospital had "received significantly less than the recommended dose of a chemotherapy drug". This week, it emerged more than 100 people were treated with the same low dose.

The oncologist at the heart of the scandal used off-protocol doses of carboplatin chemotherapy treatment, giving each of his patients a flat 100mg. The government's report stated:

> *It would be expected that, on a population basis, a failure to adhere to protocol puts every person at risk of higher rates of cancer recurrence and overall mortality.*

Without knowing the patients' medical details, we can't say whether the doctor's chosen treatment method was inadequate in treating their cancer. But we can say there is no existing evidence a flat

Author

Ian Haines
Adjunct Clinical Associate Professor, AMREP Department of Medicine, Alfred Hospital, Melbourne & Senior Medical Oncologist and Palliative Care Physician, Melbourne Oncology Group, Cabrini Haematology and Oncology Centre, Wattletree Road, Malvern, Monash University

carboplatin dose of 100mg provides inferior outcomes; particularly when it is given together with radiation therapy, called chemoradiation.

As the NSW report states, the 100 or so patients treated with low doses of carboplatin were receiving chemoradiation.

Most cancer treatment is individualised – patients receive doses based on gender, height, weight and other factors. But there are many other treatments, such as the oestrogen-blocking drug tamoxifen used in breast cancer, where everyone receives an identical dose.

What's the actual evidence?

Despite years of research, we still don't know the best dose of carboplatin to use in any patient. The specific carboplatin dose for each patient is determined in one of two ways. The first is based on how much is circulating in their system (called Area Under the Curve, or AUC). Alternatively, it is based on their body surface area (BSA).

One study evaluated four carboplatin doses in head and neck cancer. It found the efficacy for the lowest dose (AUC 3.5 every three weeks for two doses) was equal to that at the highest dose (AUC 5 every three weeks for two doses).

Usually, chemotherapy's main role is to kill cells. But when given with radiation treatment, it has a secondary purpose, which is to sensitise cells to the radiation. Low-dose chemotherapy in this instance appears to change the structure and function of cells, without severely damaging them, making them more susceptible to the lethal effects of the primary radiation treatment.

In India, which has a high incidence of head and neck cancer, a flat dose as low as 150mg has been used in a randomised trial and compared to radiation alone. The remission rates were almost doubled and comparable with higher doses of carboplatin or cisplatin.

In cases such as these, the radio-sensitising chemotherapy is the support treatment and must not increase the treatment toxicity to a level that delays the primary radiation treatment. Recent data reveals it is the completion of the scheduled radiotherapy within the defined protocol time, and not the completion of the protocol chemotherapy, that determines the outcome for patients.

There are several protocols

Protocols are created using evidence-based treatments that have been tested in clinical trials and found to be as good as, or better than, current standard treatment. There are many possible drugs and combinations of drugs for most cancers, all given at different doses and for differing lengths of time.

As the NSW government's report states, treatment of combined chemotherapy and radiation is considered the best treatment for localised head and neck cancers. Although carboplatin is at times

considered the third-line chemotherapy choice, there is a good amount of evidence it is equivalent in efficacy and less toxic than the more popular cisplatin.

The NSW report states treatment options for locally advanced cancer are clearly outlined in the National Comprehensive Cancer Network guidelines and in the eviQ Cancer Treatments Online information.

But eviQ has a list of possible treatment protocols for patients with locally advanced head and neck cancer, which includes six very different chemotherapy protocols. Under the heading of *Definitive Chemoradiation* in the medical oncology section, one of the options is to use carboplatin at a calculated dose of AUC 1.5. This would give a range of doses for varying individuals from 100mg to over 250mg.

In its radiation oncology section, there are also six protocols for chemoradiotherapy. The option with carboplatin has the dose as AUC 2 (giving doses of 150mg to over 350mg). As with many medical treatments, different oncology units choose different protocols depending on various considerations.

They are all acceptable because there is no evidence that one is better than the other. Confusingly, the two carboplatin doses here differ by 33% and the NSW report states a deviation of more than 25% either way in the protocol dose of carboplatin is unacceptable.

Why all the confusion?

The confusion often arises because early phase one and two trials of cancer drugs are designed to establish the "maximum tolerated doses" (MTD) and anti-cancer activity of the drug, or tumour response rates, in highly selected patients.

However, while there is a dose-response relationship for many chemotherapy drugs in cancer, shrinking cancers a little bit more with higher and more toxic doses rarely has meaningful benefits for patients in randomised phase three studies.

Despite the lack of evidence about dose, no oncologist or patient wants to give or receive sub-optimal treatment; most will invariably err on the side of too much rather than too little just to be safe.

The belief that more chemotherapy must be better has underpinned cancer treatment protocols and research for more than 40 years. But we've moved past that. A recent Cochrane review, for instance, found treating breast cancer with a very high dose of chemotherapy doesn't improve survival any more than if using a standard dose.

As an editorial in the Journal of Clinical Oncology stated in 2000:

> *A new paradigm for dosing chemotherapy ... uses low-dose continuous chemotherapy ... More is not always better, and this is high time for low-dose.*

The St Vincent's Hospital episode is an opportunity for all involved in caring for patients with cancer to re-examine the evidence underpinning current practice and protocols.

Cancer Chemotherapy Radiotherapy

search

search InSight

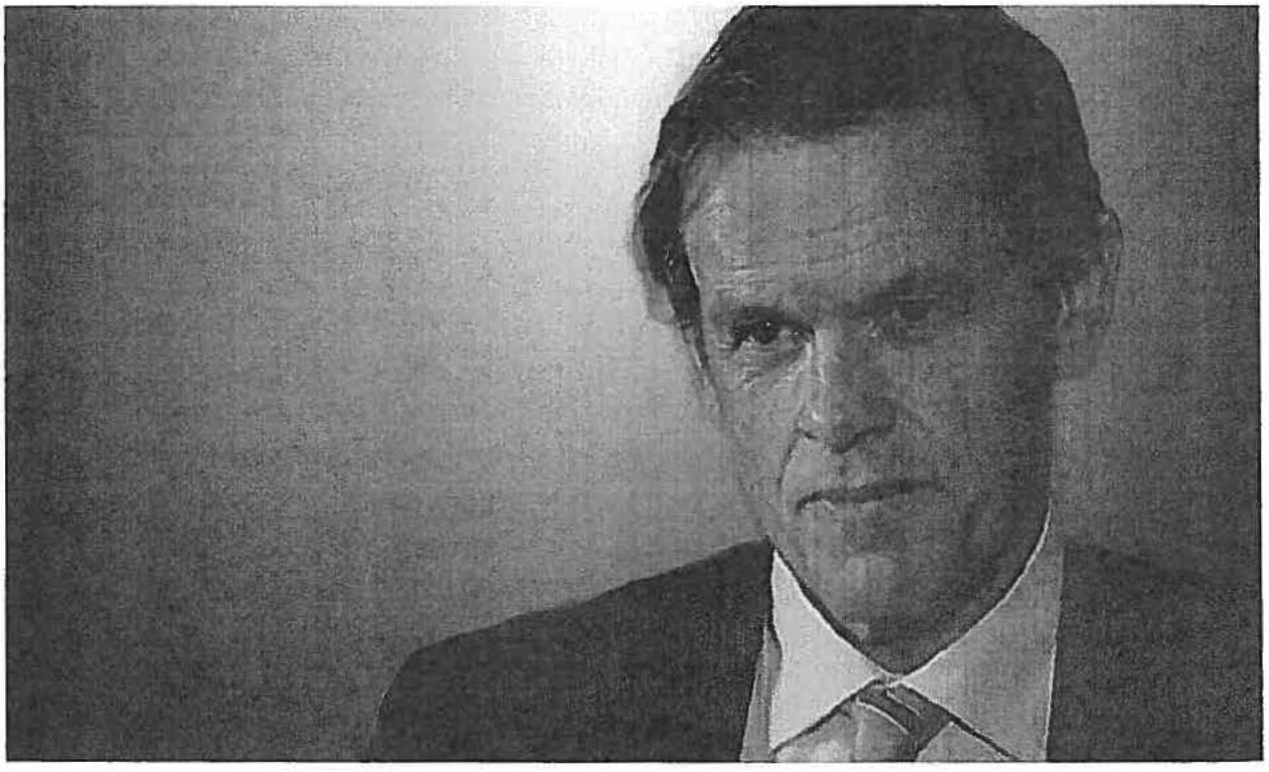
more_vert

search

search InSight

10 October 2016

Chemotherapy: more is often not better



Authored by
IAN HAINES

Related Links

Valuing the benefits of new anticancer drugs
MJA PERSPECTIVE
(https://www.mja.com.au/journal/2016/204/11/valuing-benefits-new-anticancer-drugs)

Do teleoncology models of care enable safe delivery of chemotherapy in rural towns?
MJA RESEARCH

Therefore, the belief by some that it would be expected that on a population basis, a failure to adhere to "the protocol chemotherapy dose" is likely to result in higher rates of local recurrence and higher overall mortality may not necessarily be true. Its veracity depends on the strength of the evidence underpinning the protocol.

An example of this is the much discussed treatment used at St Vincent's Hospital, Sydney, of combined carboplatin-based chemotherapy given as a concurrent radio–sensitiser in locally advanced head and neck cancer, which has certainly been established as a reasonable standard of care (here (https://www.ncbi.nlm.nih.gov/pubmed/9165134), here (http://www.redjournal.org/article/S0360-3016(13)03365-8/abstract), here (https://www.ncbi.nlm.nih.gov/pubmed/17467265), and here (https://www.ncbi.nlm.nih.gov/pubmed/23485743)).

The controversial part was the non-protocol low flat dose of carboplatin employed, and whether patients were undertreated.

Surprisingly, despite many years of research, we still don't know the best dose of carboplatin to use in any patient. One study evaluated various doses of carboplatin in head and neck cancer and found that the efficacy for the lowest dose compared favourably to the highest one (https://www.ncbi.nlm.nih.gov/pubmed/16477924). The minimum effective dose has still not been established for carboplatin and may be much lower than is conventionally used.

In addition, chemotherapy given with radiation is probably not acting primarily as a cytotoxic and is very effective at low dose because it "sensitises" the cells to radiation by a variety of mechanisms (here (https://www.ncbi.nlm.nih.gov/pubmed/17259930) and here (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074875/)). The radio-sensitising chemotherapy is the support treatment and must not increase the treatment toxicity to the level that it delays the primary radiation treatment. Recent data reveal that it is the completion of the scheduled radiotherapy within the defined protocol time and not the completion of the protocol chemotherapy that determines the outcome (https://www.ncbi.nlm.nih.gov/pubmed/26322252).

In view of these considerations, it will be important to analyse if the long term outcomes of the patient group treated at St Vincent's Hospital differ significantly from an equivalent risk group based on the best available literature of evidence-based treatment during the same period. It will be impossible to do this assessment for individual patients.

As a high-profile lead editorial in the *Journal of Clinical Oncology* stated in 2000 (https://www.ncbi.nlm.nih.gov/pubmed/10944125): "A 'new' paradigm for dosing chemotherapy ... [uses] low-dose continuous chemotherapy ... Public or underwriter pressure, allure of high-dose therapy, and technical capabilities for the sake of technology (eg, supportive care) should not drive the treatment algorithms unless they are based on sound scientific data. More is not always better, and this is high time for low-dose."

The St Vincent's Hospital episode is a good opportunity for all of us involved in caring for patients with cancer to re-examine the evidence underpinning current practice.

Clinical Associate Professor Ian Haines is a medical oncologist with the Alfred Medical Research and Education Precinct's Department of Medicine at Monash University and Cabrini Health, in Melbourne.

Radiotherapy and Oncology 92 (2009) 4–14

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Meta analysis

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon [a,*], Aurélie le Maître [a], Emilie Maillard [a], Jean Bourhis [b], on behalf of the MACH-NC Collaborative Group [1]

[a] Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France
[b] Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France

ARTICLE INFO

Article history:
Received 6 April 2009
Received in revised form 17 April 2009
Accepted 19 April 2009
Available online 14 May 2009

Keywords:
Meta-analysis
Systematic review
Individual patient data
Randomised clinical trials
Chemotherapy
Radiotherapy
Head and neck cancer

ABSTRACT

Background: Our previous individual patient data (IPD) meta-analysis showed that chemotherapy improved survival in patients curatively treated for non-metastatic head and neck squamous cell carcinoma (HNSCC), with a higher benefit with concomitant chemotherapy. However the heterogeneity of the results limited the conclusions and prompted us to confirm the results on a more complete database by adding the randomised trials conducted between 1994 and 2000.
Methods: The updated IPD meta-analysis included trials comparing loco-regional treatment to loco-regional treatment + chemotherapy in HNSCC patients and conducted between 1965 and 2000. The log-rank test, stratified by trial, was used to compare treatments. The hazard ratios of death were calculated.
Results: Twenty-four new trials, most of them of concomitant chemotherapy, were included with a total of 87 trials and 16,485 patients. The hazard ratio of death was 0.88 ($p < 0.0001$) with an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction ($p < 0.0001$) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the hazard ratio was 0.81 ($p < 0.0001$) and the absolute benefit 6.5% at 5 years. There was a decreasing effect of chemotherapy with age ($p = 0.003$, test for trend).
Conclusion: The benefit of concomitant chemotherapy was confirmed and was greater than the benefit of induction chemotherapy.
 Radiotherapy and Oncology 92 (2009) 4–14

Head and neck (oral cavity, oropharynx, hypopharynx, and larynx) squamous cell carcinomas (HNSCC) occur frequently with over 500,000 new cases diagnosed worldwide each year [1]. Our previous individual patient data meta-analysis of randomised trials showed that chemotherapy improved survival in non-metastatic HNSCC treated by surgery and/or radiotherapy (hazard ratio [HR] of 0.90, 95% confidence interval [CI] 0.85–0.94) with an overall 4% benefit at 5 years, from 32% to 36% [2]. Chemotherapy can be administrated before, at the same time or after loco-regional treatment corresponding to induction, concomitant or adjuvant chemotherapy. A greater benefit (8%) was observed in trials that gave chemotherapy concomitantly to radiotherapy. The meta-analysis pooled the data from trials performed between 1965 and 1993. Cisplatin started to be used in head and neck randomised trials in the early 80s. The observed heterogeneity of the results required cautious conclusions; indeed, five trials which represented about 7% of the data explained most of the heterogeneity and when they were excluded the higher benefit of concomitant chemotherapy disappeared [3]. Therefore the MACH-NC group decided to confirm the results by updating its database with the inclusion of the randomised trials performed between 1994 and 2000. Preliminary results were published in 2007 in a short report [4].

Materials and methods

The methods were pre-specified in a protocol (copy available on request).

Eligibility criteria

Trials were eligible if they had accrued previously untreated patients with HNSCC and compared loco-regional treatment with loco-regional treatment plus chemotherapy. Each trial had to be randomised in a way that those entering patients could not know in advance which treatment an individual would receive (avoiding the potential of allocation bias). Trials were eligible if accrual was

* Corresponding author. Address: Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, 39 rue Camille Desmoulins, 94 805 VILLEJUIF cedex, France.
E-mail address: jppignon@igr.fr (J.-P. Pignon).
[1] Collaborators listed at the end of the paper.

0167-8140/$ - see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2009.04.014

completed before 31st December 2000, and if all randomised patients had undergone a potentially curative loco-regional treatment and had not been treated for another malignancy. Trials concerning tumours of the oral cavity, oropharynx, hypopharynx and larynx were included. Trials including only nasopharyngeal carcinomas were excluded.

Identification of trials

To avoid publication bias, both published and unpublished trials were included. Searches of Medline, Clinprot and Embase were supplemented with hand searches of meeting abstracts (ASCO, ESTRO, ASTRO, ESMO, ECCO) and references in review articles. Trial registers (PDQ, ClinProt, CCT mega-register) were consulted. Experts and all trialists who took part in the meta-analysis were also asked to identify trials.

Data

The data collected for each patient were: age, sex, tumour site, TNM or stage, performance status, treatment allocated, and date of randomisation. The date and site of the first recurrence, the date of second primary cancer and the cause of death were also collected. This last variable was only available for the recent trials. Updated information on survival status and date of last follow-up were collected.

All data were checked for internal consistency and were compared with the trial protocol and published reports. Range checks were performed and extreme values were verified with the trialists. Each trial was analysed individually, and the resulting survival analyses along with trial data were sent to the trialists for review.

Analysis

The main endpoint was overall survival. Event-free survival, cumulative loco-regional, and distant failure were secondary endpoints as were cancer and non-cancer mortality. Deaths attributed to causes other than head and neck cancer with no reported recurrence of head and neck cancer were described as "non-head and neck cancer deaths". All other deaths were described as "head and neck cancer deaths" including deaths from head and neck cancer, deaths from any cause after recurrence and deaths from unknown cause without reported recurrence.

All analyses were carried out on an intention-to-treat basis, i.e., all randomised patients were analysed in the allocated treatment group, irrespective of their actual treatment. Trials were divided into three groups according to the timing of chemotherapy: adjuvant, induction (also called neo-adjuvant) and concomitant as previously described [2].

Statistics

The median follow-up time was computed according to the reverse Kaplan Meier method by censoring deaths and using as events those censored in the Kaplan Meier method [5]. Survival analyses were stratified by trial, and the log-rank observed minus expected number of deaths ($O - E$) and its variance were used to calculate individual and overall pooled hazard ratios (HRs) using a fixed effect model [6]. To prevent late recurrences from biasing the analyses of cause-specific mortality, the log-rank analysis of non-head and neck cancer mortality covered only the period before recurrence (i.e., data are censored at the first recurrence) [7]. An unbiased – although potentially diluted – log-rank analysis of head and neck cancer mortality was obtained indirectly by subtracting the log-rank statistic for non-head and neck cancer mortality from the log-rank statistic for mortality from all causes (i.e., the two observed values are subtracted from each other, the two expected values are subtracted from each other, and the two variances are subtracted from each other). Then, this method takes into account the competing risk between the two types of mortality. Heterogeneity between trials and groups was investigated using Chi-square tests [8] and the I^2 index [9] that expresses the percentage variability of the results related to heterogeneity rather than to the sampling error. To study the interaction between treatment and a covariate, an analysis stratified by trial was performed for each covariate group, and the HRs for each covariate group (e.g. men and women), were compared by a test for interaction or trend as appropriate. Stratified survival curves were computed for control and experimental groups and were used to calculate absolute benefit at 2, and 5 years [10]. The absolute benefit depends on hazard ratio and survival rate. All p-values were two sided.

Results

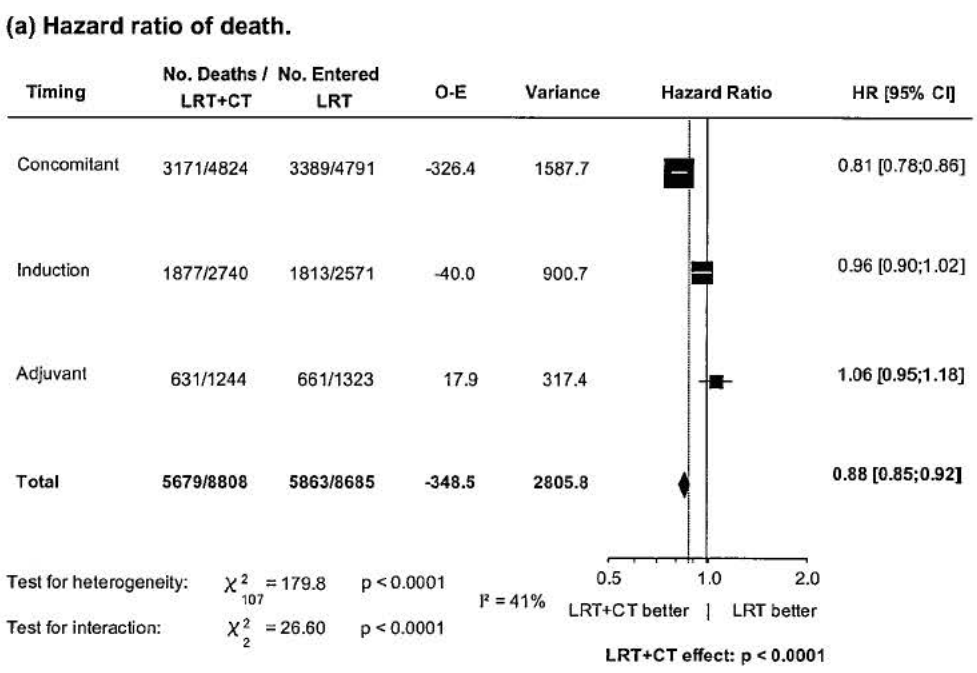
The meta-analysis included 87 randomised trials (16,485 patients) comparing loco-regional treatment versus the same loco-regional treatment + chemotherapy. The trials included in the previous MACH-NC meta-analysis have been described previously [2]. Twenty-four new trials (5744 patients) evaluated chemotherapy concomitant with radiotherapy. One trial [5 of the Web-appendix] evaluated both adjuvant and concomitant chemotherapy. Data from one trial [11] that included 86 patients were lost, and two trials [12] including 2172 patients were excluded after blind review because of potential bias in patients follow-up. Two trials (EORTC 22954 and 22962, 116 patients) were unpublished. We were able to collect data from 655 of the 791 randomised patients that had been excluded from the original published analyses. Updated follow-up was obtained for most of the trials and the overall median follow-up was 5.6 years. Because some trials had strata that corresponded to different loco-regional treatments or chemotherapies, and because some trials had 3-arms or a 2 by 2 design, some trial arms were utilised twice, such that the number of comparisons in the meta-analysis was 108 and the number of patients was 17,493. The description of the new trials included and their references can be found in Web-Table 1. The distribution of the treatment comparison according to timing of chemotherapy, type of loco-regional treatment, type of chemotherapy and period of accrual is given in Web-Table 2. The description of the overall population is given in Web-Table 3.

Effect of concomitant chemotherapy

The following analyses concern the 50 concomitant trials including 9615 patients (6560 deaths) with a median follow-up of 5.6 years.

Overall and event-free survival

The hazard ratio of death (Fig. 1a and Web-Fig. 1) was 0.81 (95% confidence interval: 0.78–0.86; $p < 0.0001$) in favour of chemotherapy with an absolute benefit of 6.5% at 5 years (Fig. 2a). The magnitude of the benefit was identical for the 1965–1993 trials and the 1994–2000 trials, without significant heterogeneity ($p = 0.27$) in the most recent trials. Excluding trials with less than 80 patients, or performed before 1980, or with a follow-up shorter than 5 years led to similar results (sensitivity analysis, Web-Table 4a). Analysis without arm duplication led to similar results (Web-Table 4a). In the recent trials, it was possible to separate cancer and non-cancer deaths. Cause of death was missing in less than 4% of the patients without recurrence. The benefit of chemotherapy was due to its effect on deaths related to head and neck cancer (HR 0.78 [0.73–0.84], $p < 0.0001$; Fig. 3) and with no effect on non-cancer deaths (0.96 [0.82–1.12], $p = 0.62$).



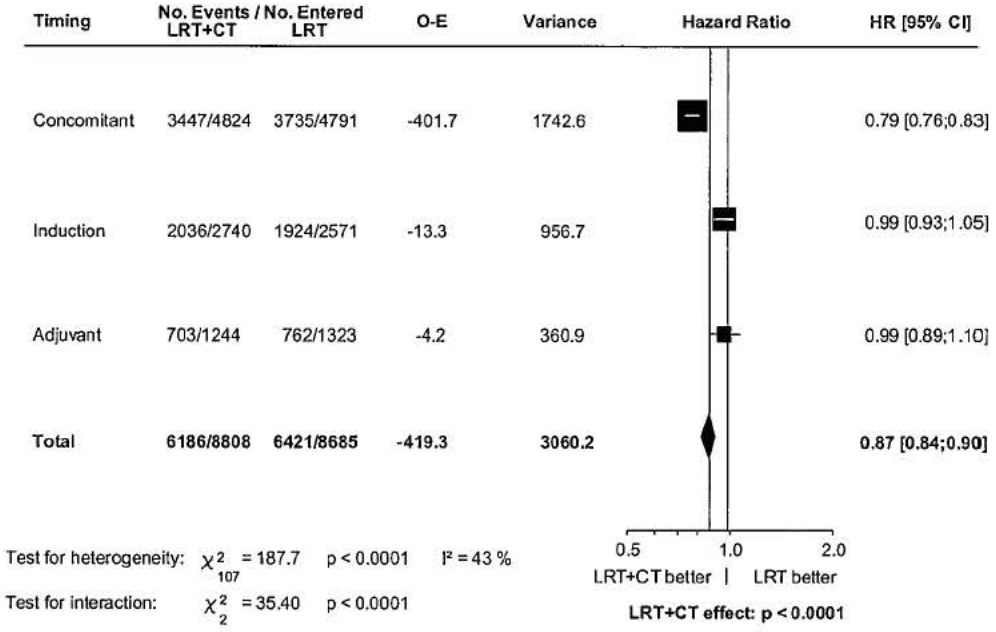
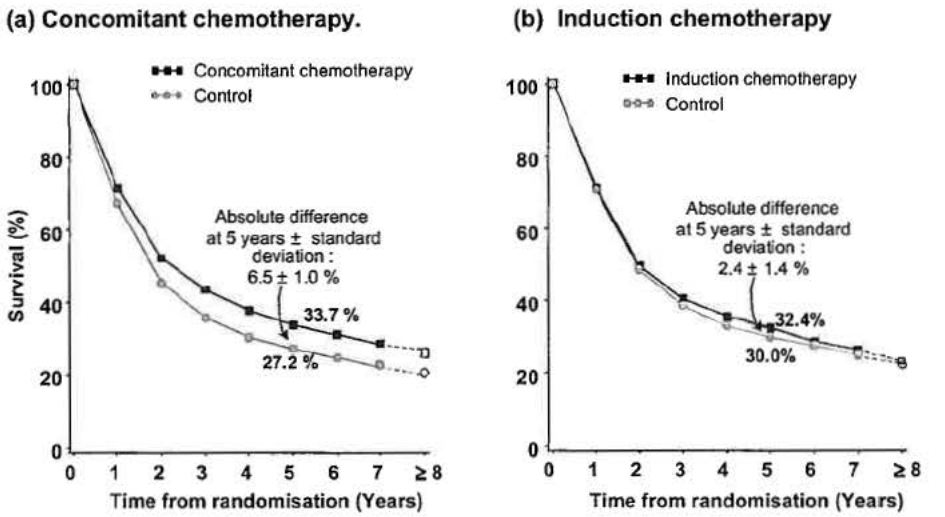


Fig. 1. Hazard ratio with loco-regional treatment plus chemotherapy versus loco-regional treatment alone by timing of chemotherapy. (a) Hazard ratio of death; (b) hazard ratio of recurrence or death. The broken line and centre of the black diamond correspond to overall pooled hazard ratio (HR) and the horizontal tip of the diamond is the 95% confidence interval (CI). The centre of black square corresponds to the HR of different types of chemotherapies. The area of the square is proportional to the number of deaths in each trial (or group of trials). CT, chemotherapy; LRT, loco-regional treatment; RT, radiotherapy; $O - E$, observed minus expected.

Similar results were observed for event-free survival, with a hazard ratio of 0.79 (0.76–0.83; $p < 0.0001$, Fig. 1b) and an absolute benefit of 6.2% at 5 years (from 23.1% to 29.3%).

Subset analyses

The benefit of chemotherapy on survival did not differ significantly (test for interaction, $p = 0.14$) between the group of trials with postoperative radiotherapy (HR 0.79 [0.68–0.91]), or curative radiotherapy with conventional (HR 0.83 [0.78–0.88]) or altered fractionation (HR 0.73 [0.65–0.82]; Web-Table 5). No significant difference ($p = 0.19$) was seen between mono-chemotherapy (HR 0.84) and poly-chemotherapy (HR 0.78). In the poly-chemotherapy group, the effect of chemotherapy was not significantly different ($p = 0.41$) between the different sub-groups: with cisplatin or carboplatin (platin) and 5-fluorouracil (5-FU), with either platin or 5-FU or with neither (Fig. 4). In the mono-chemotherapy group, the

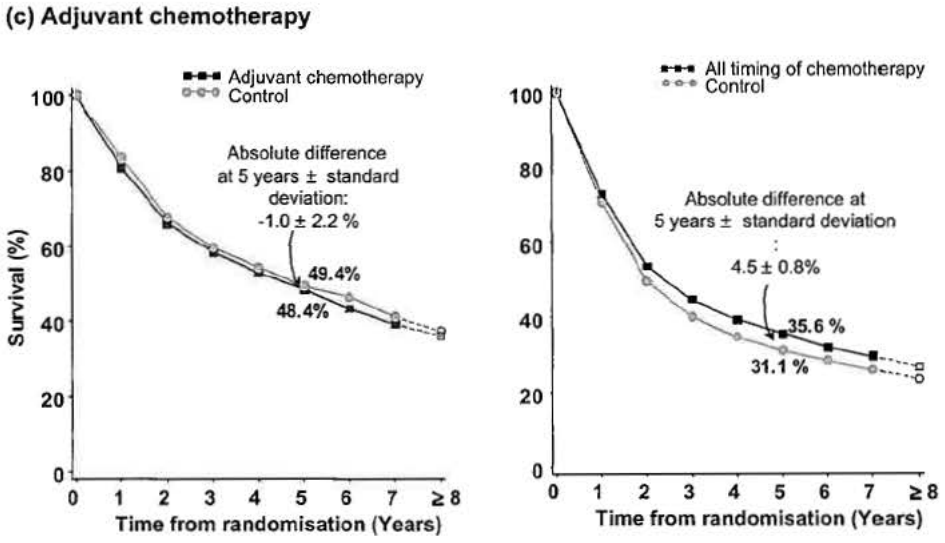


Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	2500/6298	672/3658	217/2487
Chemotherapy	2187/6647	706/4576	278/3194

Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	1283/3535	393/2276	137/1417
Chemotherapy	1318/3820	392/2608	167/1530



Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	417/2107	181/1653	63/729
Chemotherapy	403/1956	158/1528	70/718

Death/person-years by period

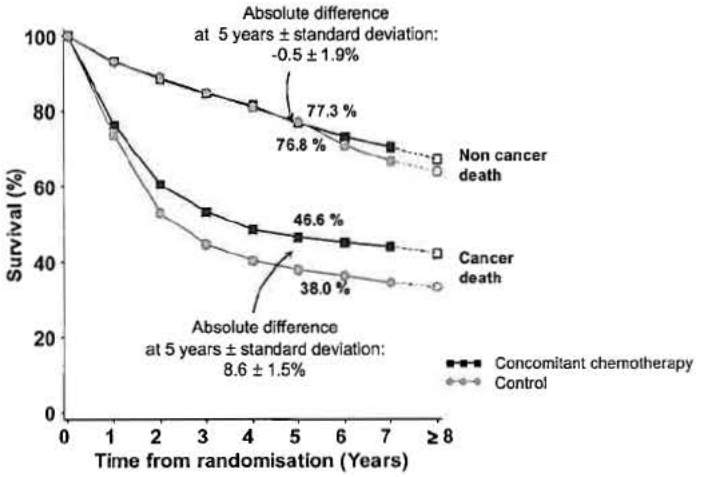
	Years 0-2	Years 3-5	Years ≥ 6
Control	4200/11939	1246/7587	417/4633
Chemotherapy	3908/12425	1256/8712	515/5443

Fig. 2. Survival curves by treatment arm for all trials and for the three groups of trials according to the 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. (a) Concomitant chemotherapy; (b) induction chemotherapy; (c) adjuvant chemotherapy; (d) all three groups together. Absolute differences are given with their standard error.

effect of chemotherapy was significantly higher ($p = 0.006$) with platin than with other types of mono-chemotherapies (Fig. 4). Only five trials used carboplatin: two alone, and three with 5-FU (Web-Table 1 and Reference 2).

Sub-group analyses

Fig. 5 shows the effect of chemotherapy on survival according to patient characteristics. The only statistically significant result was a decreasing effect of chemotherapy on survival with increasing age (test for trend, $p = 0.003$; Fig. 5b). This effect could not be explained by an imbalance in the other covariates studied (data not shown). There was no significant variation of chemotherapy effect according to patient characteristics for event-free survival (data not shown). The cause of death was available only for the recent trials (1994–2000) and varied markedly according to age. As might be expected, the proportion of deaths not due to head and neck cancer increased progressively with age from 15% in patients less than 50–39% in patients 71 and over.



Non cancer death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	187/2985	86/1769	37/544
Chemotherapy	201/3301	106/2330	34/727

Cancer death by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	1268	290	32
Chemotherapy	1049	278	28

Fig. 3. Non-cancer death and cancer death survival curves in the recent trials comparing loco-regional treatment plus concomitant chemotherapy with loco-regional treatment alone.

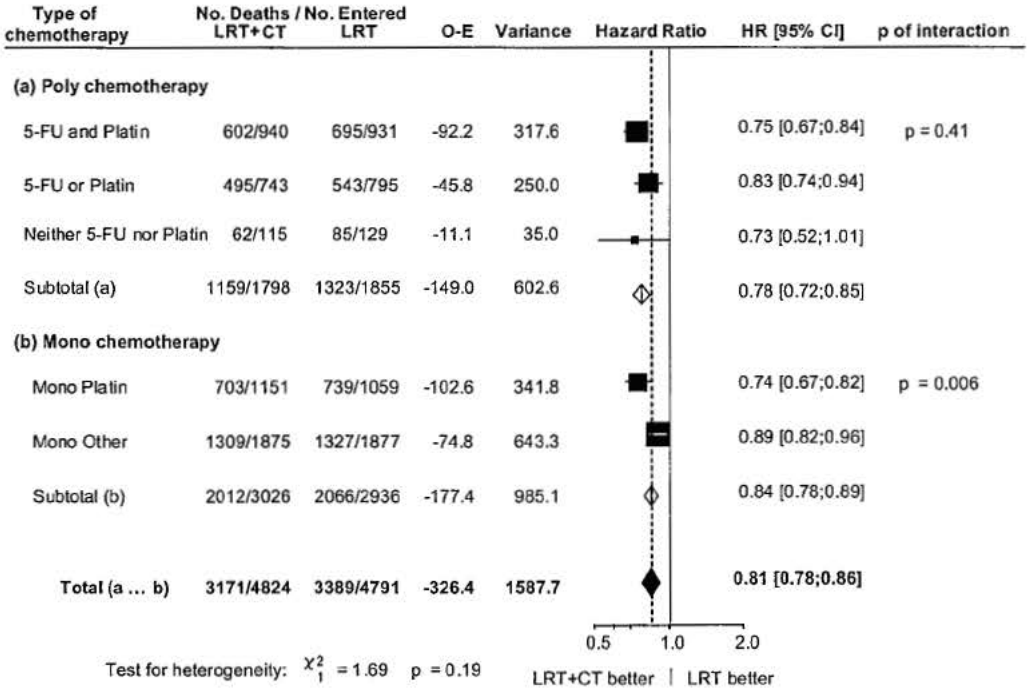


Fig. 4. Hazard ratio of death with loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone by type of chemotherapy. CT, chemotherapy. The test of heterogeneity on the bottom corresponds to the comparison of the HRs for poly and mono-chemotherapy. The tests of interaction on the right correspond to the comparison of the HR of the type of chemotherapy within the poly-chemotherapy and mono-chemotherapy groups of trials.

Effect of induction chemotherapy

The following analyses concern 31 induction chemotherapy trials including 5311 patients (3690 deaths) with a median follow-up of 6.1 years. The HR of death (Fig. 1a and Web-Fig. 2) was 0.96 ([0.90–1.02] $p = 0.18$) in favour of induction chemotherapy with an absolute benefit of 2.4% at 5 years (Fig. 2b). There was no significant ($p = 0.23$) variation of the effect according to the type of chemotherapy: 0.90 (0.82–0.99) for 5-FU-platin, 1.01 (0.91–1.12) for

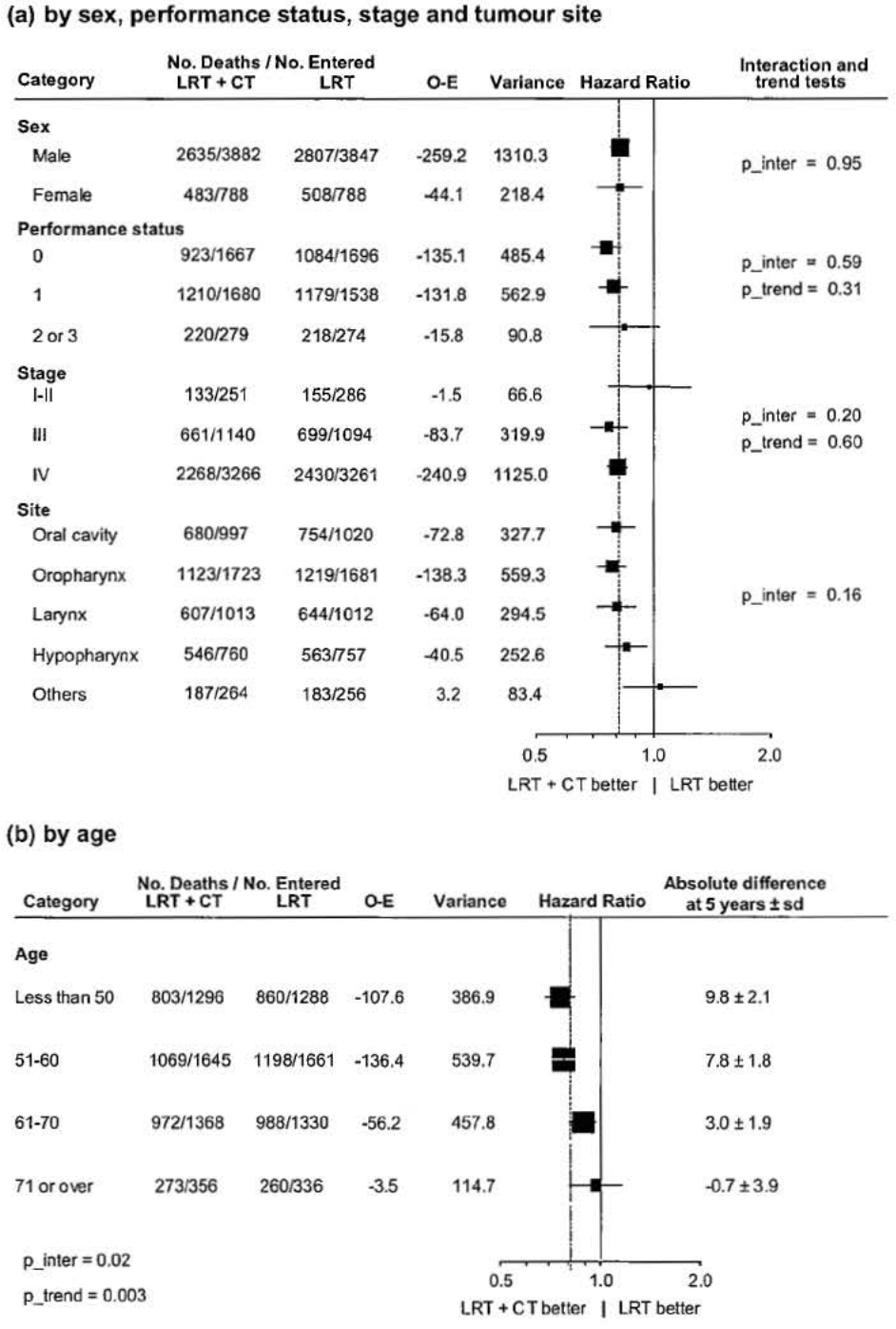


Fig. 5. Hazard ratio of death with loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone by patient characteristics. (a) By sex, performance status, stage and tumour site; (b) by age. *p_heter*: *p*-value of the test of heterogeneity, *p_trend*: *p*-value of the test for trend.

other poly-chemotherapy, 0.99 (0.84–1.18) for mono-chemotherapy (no trial with platin). Sensitivity analyses are reported in Web-Table 4b. Similar results were observed for event-free survival, with a hazard ratio of 0.99 (0.93–1.05; $p = 0.67$) and an absolute benefit of 1.3% at 5 years (from 26.3% to 27.6%). The hazard ratios of death were not significantly different ($p = 0.68$) between trials using radiotherapy alone, surgery plus postoperative radiotherapy or other loco-regional treatment (Web-Table 5). There was no clear evidence of a differential effect of induction chemotherapy on survival according to age, sex, performance, stage or tumour site.

Comparison of concomitant and induction chemotherapy

Direct comparison

This analysis concerns the 6 randomised trials which have used the same drugs in both arms, and compared the timing of their use relatively to radiotherapy. These trials have included a total of 861

patients (717 deaths) with a median follow-up of 10.9 years. The trials and the patients of this analysis have been described previously [2]. Data for event-free survival and loco-regional failure were available for 5 trials. Data on distant failure were missing for most of the trials. The three endpoints studied (Fig. 6) showed results in favour of the concomitant group: hazard ratio of 0.90 for overall survival ($p = 0.15$) with an absolute benefit of 3.5% at 5 years (from 24.3 to 27.8; Fig. 6b); hazard ratio of 0.81 for event-free survival ($p = 0.01$); hazard ratio of 0.77 for loco-regional failure ($p = 0.005$). The corresponding hazard ratio plots are given in Web-Fig. 4a, b and c.

Indirect comparison

This analysis is based on the comparison of the chemotherapy effect observed in the 50 concomitant chemotherapy trials and in 31 induction chemotherapy trials mentioned above.

Overall survival

The observed benefit of chemotherapy was significantly greater in the concomitant group (HR 0.81 [0.78–0.86]) than in the induction group (HR 0.96 [0.90–1.02]; test for interaction $p < 0.0001$). A significant difference was also observed in favour of concomitant chemotherapy when the analysis included only trials with 5-FU-platin ($p = 0.01$).

Cumulative loco-regional and distant failure

Data on loco-regional failure were available for 50 concomitant and 30 induction trials, respectively, whereas the data for distant metastasis were available for 44 concomitant and 26 induction trials, respectively. Regarding loco-regional failure, the benefit of concomitant chemotherapy was significant (HR 0.74 [0.70–0.79] $p < 0.0001$; p for heterogeneity 0.006; $I^2 = 34\%$), but there was no such effect of induction chemotherapy (HR 1.03 [0.95–1.13]; $p = 0.43$; p for heterogeneity $p < 0.0001$; $I^2 = 63\%$; Fig. 7a). The two hazard ratios were significantly different ($p < 0.0001$) in favour of the concomitant group. The difference between concomitant and induction chemotherapies was even more pronounced when the combination of 5-FU-platin was considered (HR 0.66 versus 1.02, $p < 0.0001$, Fig. 7b). Regarding distant failure, the benefit of concomitant chemotherapy appeared significant with a hazard ratio of 0.88 [0.77–1.00] $p = 0.04$; p for heterogeneity 0.39; $I^2 = 4\%$; Fig. 7a) whereas the benefit of induction chemotherapy was also

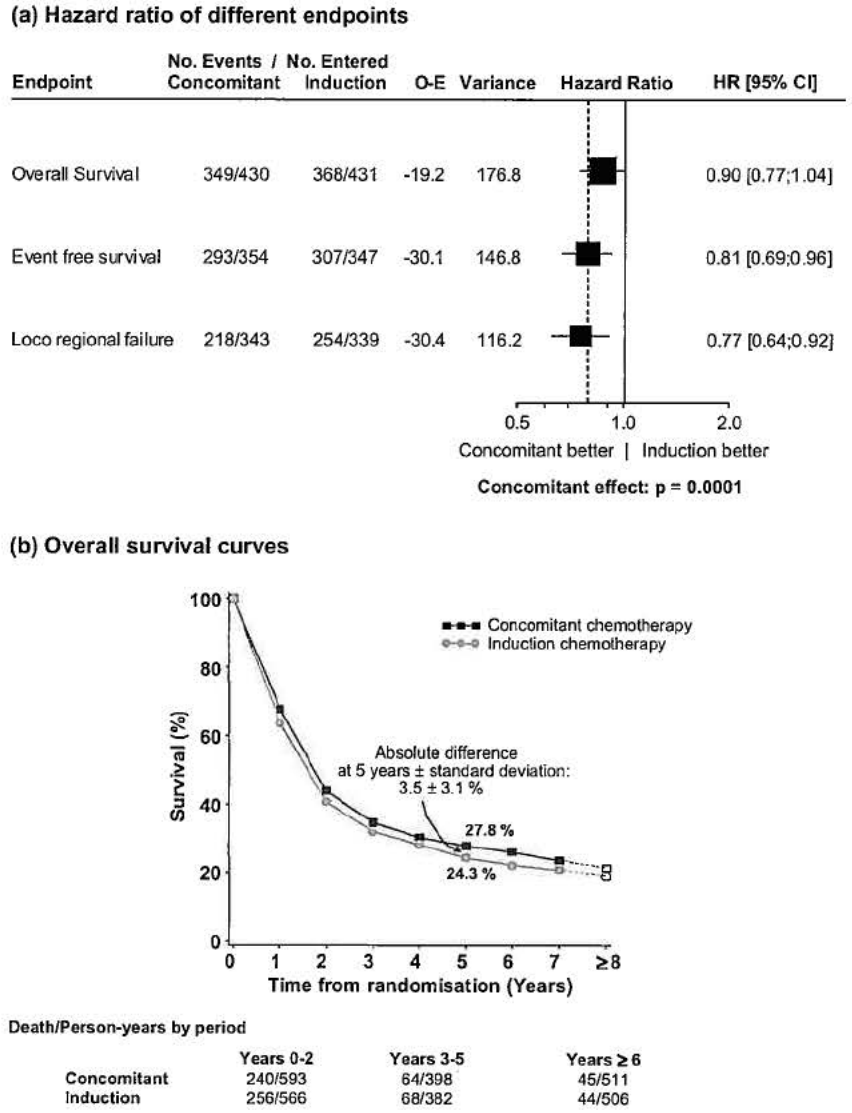
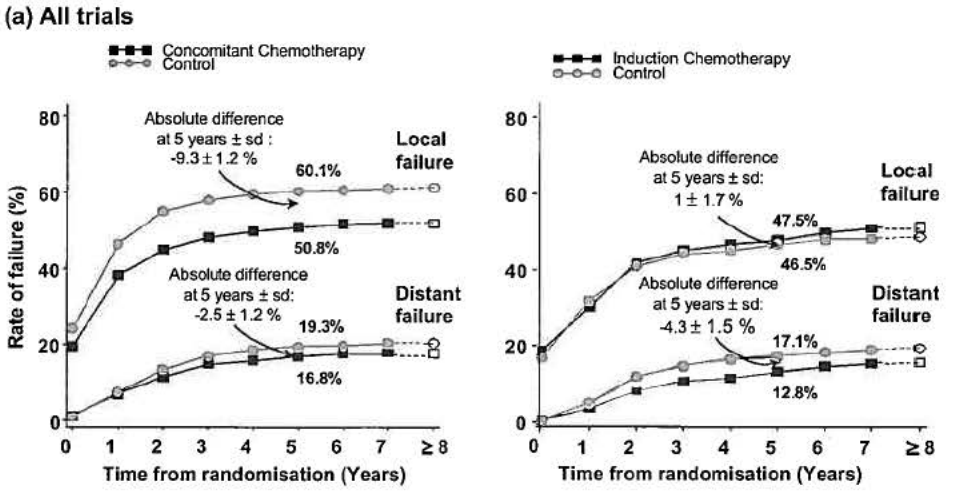
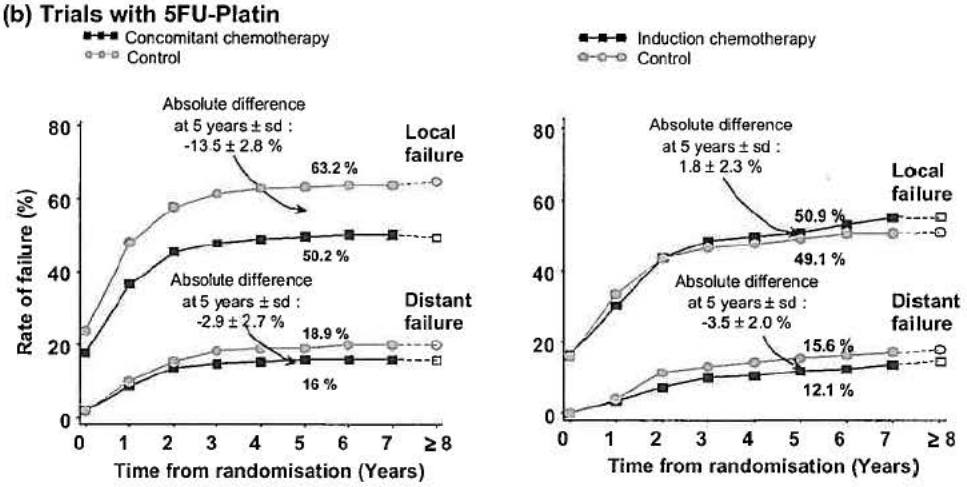


Fig. 6. Direct comparison of loco-regional treatment plus concomitant chemotherapy with loco-regional treatment plus induction chemotherapy. (a) Hazard ratio of different endpoints; (b) overall survival curves.



Local failure and distant failure /person-years by period

	Years 0-2	Years 3-5	Years ≥ 6	Years 0-2	Years 3-5	Years ≥ 6
Local failure						
Control	2509/8969	127/2812	18/2016	942/5335	70/1897	16/1202
Chemotherapy	2045/9789	162/3881	21/2822	1049/5737	85/2165	27/1245
Distant failure						
Control	382/9817	82/3026	9/2195	183/5717	45/2025	11/1328
Chemotherapy	370/10438	96/4010	10/2896	143/6207	46/2329	16/1391



Local failure and distant failure /person-years by period

	Years 0-2	Years 3-5	Years ≥ 6	Years 0-2	Years 3-5	Years ≥ 6
Local failure						
Control	493/1648	22/406	2/165	497/2627	38/1073	10/684
Chemotherapy	373/1837	20/603	1/240	519/2749	58/1142	22/751
Distant failure						
Control	82/1756	8/416	1/166	90/2788	18/1116	8/711
Chemotherapy	83/1915	6/616	0/241	62/2929	23/1204	9/773

Fig. 7. Loco-regional and distant failure cumulative rates in trials comparing loco-regional treatment plus concomitant with loco-regional treatment alone and induction chemotherapy with loco-regional treatment alone. (a) All type of chemotherapy; (b) 5-FU-platin. sd, standard deviation.

significant and more pronounced (HR 0.73 [0.61–0.88], $p = 0.001$; p for heterogeneity 0.19; $I^2 = 19\%$). The comparison of the two hazard ratios was not significant ($p = 0.12$ for all trials, $p = 0.56$ for 5-FU-platin trials, Fig. 7b).

Overall effect of adding chemotherapy to loco-regional treatment

As shown in Figs. 1 and 2, a significant benefit of chemotherapy ($p < 0.0001$) was observed for overall survival (HR 0.88, 0.85–0.92), with an absolute improvement of 4.5% in 5 years survival. There was a heterogeneity of chemotherapy effect between trials ($p < 0.0001$; $I^2 = 41\%$) which was observed only in the concomitant group ($p = 0.0001$, $I^2 = 45\%$). A larger effect of chemotherapy was observed in the concomitant trials than in the other two groups (test for interaction $p < 0.0001$; Figs. 1 and 2). There was no good evidence of an effect of chemotherapy for induction or adjuvant (HR 1.06 [0.95–1.18] $p = 0.32$; $I^2 = 10\%$) chemotherapy. The detailed HR plots for each type of

chemotherapy are shown in Web-Figs. 1–3. There was no variation of the chemotherapy effect on overall survival according to loco-regional treatment among each chemotherapy timing trial group (Web-Table 5).

Similar results were observed for event-free survival (Fig. 1b), both for the whole population and for the three groups. For the whole population the hazard ratio was 0.87 (0.84–0.90; $p < 0.0001$) with an absolute benefit of 4.1% at 5 years (from 26.8 to 30.9%).

In an exploratory analysis, mortality at 90 days was used as a proxy of early deaths related to treatment. The hazard ratio was 1.14 (0.98–1.31; $p = 0.08$; test for heterogeneity $p = 0.30$; $I^2 = 6\%$). The excess of early death due to the chemotherapy was significantly higher in the adjuvant setting (test for interaction $p = 0.02$): HR of 2.1 (1.31–3.36) for the adjuvant group versus 1.09 and 1.03 for the concomitant and induction groups, respectively (Web-Fig. 5).

Discussion

This updated individual patient data meta-analysis provides a reliable evaluation of the effect of chemotherapy in locally advanced head and neck cancer. Compared to the previous study, a large number of patients and randomised trials have been added and the follow-up has been markedly increased, including for the older trials. Consequently, the statistical power has been increased and we were able to undertake more complete analyses with new endpoints (effect of different types of chemotherapies, effect on distant versus local failure, etc.). Overall the current results appear stronger, compared to the previous MACH-NC meta-analysis and should be useful to determine standard treatment in this disease, as well as generating new hypotheses to be tested in future randomised trials.

Adding new data did not change the magnitude of the observed survival benefit resulting from the addition of chemotherapy, which was confirmed to be around 4%. This benefit was larger for concomitant chemotherapy, whereas there was no clear evidence of a benefit for induction and adjuvant chemotherapies. Adding the data from 24 new trials did not modify the magnitude of the relative benefit of concomitant chemotherapy from that reported previously (HR = 0.82 versus 0.81).

Importantly, there was a minimal heterogeneity between the 24 new trials ($I^2 = 34\%$), suggesting a strong consistency in the results of these randomised trials, and reinforcing the strength of the evidence of the observed benefit. In addition, the analysis of the concomitant group of trials allowed new and important conclusions to be drawn. Firstly, the fact that there was no excess of non-cancer deaths, strongly suggests that this treatment was effective in reducing cancer-related mortality without deleterious effect on death from other causes. We did not have data on compliance and toxicity.

Regarding the type of drugs to be combined concomitantly with radiotherapy, cisplatin alone, cisplatin or carboplatin associated with 5-FU or other poly-chemotherapy including either platin or 5-FU gave a benefit of the same order of magnitude. In contrast mono-chemotherapy with a drug other than cisplatin led to inferior results and should not be recommended in routine practice (Fig. 4). Single agent cisplatin appears to be one of the standard treatments in combination with radiotherapy. Most of the randomised trials have used a dose of cisplatin of 100 mg/m^2, three times throughout the course of radiotherapy (cumulative dose of 300 mg/m^2). Interestingly, the only negative "cisplatin alone" trial in this meta-analysis used a cumulative dose of 140 mg/m^2 (20 mg/m^2 × 7) [13] suggesting that the total dose of cisplatin could be important.

Another key message is that the benefit of concomitant chemotherapy appears to be similar irrespective of whether the radiotherapy was given conventionally or using altered fractionation. Finally, this meta-analysis confirmed that the magnitude of the benefit of concomitant chemotherapy is less in older patients, a feature that has also been observed with altered fractionation compared to conventional radiotherapy in head and neck cancer [14] and also when combining cetuximab plus radiotherapy [15]. One of the explanations is that older patients more frequently die from other causes than their head and neck cancer, which makes more difficult to observe the benefit in these patients (dilution effect). The absence of significant interaction with age on event-free survival is in favour of an effect on cancer death independent of age. Another explanation could be an increase in non-cancer deaths by the chemotherapy in old patients. The number of non-cancer deaths in the 71+ group was too small ($n = 93$) to study the impact of chemotherapy on non-cancer deaths.

This meta-analysis also allowed a new comparison of the benefit associated with concomitant versus induction chemotherapy. It is interesting to note that both the indirect and the direct comparisons were consistent on survival, event-free survival and loco-regional failure, showing a clear advantage in favour of concomitant chemotherapy. Indirect comparison should be interpreted with caution as the loco-regional treatment alone arm may not be comparable in the concomitant and induction trials. The 5 year survival rates in the control arm were, respectively, 27% and 30% in concomitant and induction trials.

However, one of the most striking observations was that concomitant chemotherapy had a pronounced effect on loco-regional failure, which was not observed for induction chemotherapy. On the other hand, induction chemotherapy provided a relatively more pronounced effect on distant metastases, compared to concomitant chemotherapy, suggesting the need to use a relatively high dose of chemotherapy to influence the occurrence of distant metastases. This also suggests that concomitant and induction chemotherapies may be complementary for this type of cancer and justifies the ongoing current randomised trials evaluating the benefit of adding induction chemotherapy before concomitant radio-chemotherapy. It is also important in these ongoing trials to evaluate whether induction chemotherapy adversely affects the compliance to the concomitant radio-chemotherapy part of the treatment, which appears to be the most important component of this sequential strategy. Since taxane-based induction chemotherapy also proved, in three recent randomised trials [16–18], to be superior to the reference 5-FU-platin-based induction chemotherapy, it is not possible to rule out that the benefit due to induction chemotherapy could be more pronounced that it appears to be in this meta-analysis. However, this needs to be tested in ongoing randomised trials which add induction chemotherapy to concomitant radio-chemotherapy. Finally, in locally advanced patients who received chemotherapy, the role of cetuximab, which improves the effect of radiotherapy [19], remains to be determined.

Role of the funding source

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

Investigator contribution (see list of investigator at the end of the paper)

Secretariat: J.P.P., J.B., B.L., J.L.L., J.P.A. conceived, designed and supervised the study;

J.P.P., J.B. obtained funding;

C.A., N.S., A.L.M., E.M., J.P.P. participated in data collection and checking;

C.A., A.L.M., E.M., J.P.P. did statistical analyses;

J.P.P., J.B., A.L.M., E.M. wrote the draft, with revision from the other investigator.

The authors had full access to all the data and analyses and, after consultation with the collaborators, had final responsibility for the decision to submit for publication.

Steering committee: Its members revised the protocol, contributed to the selection of the trials, and revised the manuscript.

Other investigators were trialists and contributed to the study by providing data, replying to the secretariat queries and validating the re-analysis of their trial. Most of them participated in investigator meetings on preliminary results and had the opportunity to review the manuscript.

MACH-NC Collaborative Group

Secretariat

Caroline Amand, Jean Pierre Armand, Jean Bourhis, Aurélie Le Maître, Bernard Luboinski, Emilie Maillard, Jean-Pierre Pignon, Jean-Louis Lefebvre, Nathalie Syz

Steering Committee

Jacques Bernier, Volker Budach, Arlene A. Forastiere, Lesley A. Stewart, Everett E. Vokes.

Investigators

D.J. Adelstein (Cleveland Clinic Foundation), J.P. Armand (Institut Claudius Regaud), C. Amand (Intitut Gustave-Roussy [IGR]), H. Audry (IGR), J.M. Bachaud (Institut Claudius Regaud), H.G. Bartelink (Netherlands Cancer Institute, Amsterdam), J. Bernier (Clinique de Genolier), W.R. Bezwoda (University of the Witwatersrand), A. Buffoli (Instituto di Radioterapie Oncologica, Udine), J. Bourhis (IGR), K.T. Bhowmik (Vardhaman Mahavir Medical College), D. Brizel (Duke University Medical Center), G.P. Browman (Mc Master University), V. Budach (Charité University Hospital), G. Calais (Centre Hospitalier Universitaire de Tours), B.H. Campbell (Medical College of Wisconsin), A. Carugati (Instituto de Oncología Ángel H Roffo), S. Chalkidou (Hellenic Cooperative Oncology Group), J.R. Clark (Dana Farber Cancer Institute), E. Cohen (Institut Claudius Regaud), L. Collette (European Organization for Research and Treatment of Cancer), O. Dal Canton (Ospedale S Giovanni Vecchio, Torino), D. Dalley (St. Vincent's Hospital, Sydney), J. Depondt (Centre Hospitalier Universitaire de Bichat), L. Désigné (IGR), A. Deszcz-Thomas (Centre Hospitalier Universitaire de la Pitié-Salpêtriére), B. Di Blasio (Parma University Hospital), W. Dobrowsky (University of Vienna), C. Domenge (IGR), F. Eschwege (IGR), J.F. Evensen (Norwegian Radium Hospital), C. Fallai (Università di Firenze), J.J. Fischer (Yale University), A.A. Forastière (Johns Hopkins University), G. Fountzilas (Aristotle University of Thessaloniki), K.K. Fu (University of California San Francisco), D. Gedouin (Centre Eugène Marquis), S. Guérin (IGR), F. Geara (MD Anderson Cancer Centre), R. Giglio (Instituto de Oncología Ángel H Roffo), N.K. Gupta (Christie Hospital, Manchester), E. Haddad (Hôpital Universitaire H Mondor), B.G. Haffty (Yale University), Y. Hasegawa (Aichi Cancer Centre), C. Hill (IGR), J.C. Horiot (Centre Georges François Leclerc), M. Horiuchi (Tokaï University), J. Houghton (Cancer Research Campaign & University College London Cancer Trials Centre), P. Huguenin† (Deceased) (University Hospital Zurich), P. Jan (IGR), Ch. Jaulerry (Institut Curie), B. Jeremic (Kragulevac University Hospital), T. Jouffroy (Institut Curie), A. Jortay (Brumann University Hospital), B. Kapstad (University of Bergen), L.P. Kowalski (A.C. Camargo Hospital, Sao Paulo), S. Kramer (Thomas Jefferson University Hospital), K.S. Krishnamurthi (Madras Cancer Institute), S. Kumar (Sanjay Gandhi Post Graduate Institute of Medical Science), G. Laramore (University of Washington, Seattle), E. Lartigau (Centre Oscar Lambret), J.L. Lefebvre (Centre Oscar Lambret), A. Le Maitre (IGR), T. Leong (Harvard University), F. Lewin (Huddinge University Hospital), B. Luboinski (IGR), M. Luboinski (IGR), E. Maillard (IGR), T. Maipang (Prince of Songkla University), M. Martin (Centre Hospitalier Intercommunal de Créteil), J.J. Mazeron (Centre Hospitalier Universitaire de la Pitié-Salpêtriére), M. Merlano (National Institute for Cancer Research, Genoa), S. Metha (Mumbai Group), R. Molinari (Istituto Nazionale Tumori, Milano), K. Monson (Cancer Research Campaign & University College London Cancer Trials Centre), K. Morita (Aichi Cancer centre), R.P. Mueller (University of Wuerzburg), A. Murias (Hospital Insular del Gran Canaria, Las Plamas), V. Mosseri (Institut Curie), G. Numico (National Institute for Cancer Research, Genoa), P. Olmi (Università di Firenze), B. O'Sullivan (Princess Margaret Hospital, Toronto University) J. Overgaard (Aarhus University Hospital), A. Paccagnella (SS Giovanni and Paolo Hospital, Venezia), T. Pajak (Radiation Therapy Oncology Group), L.M. Parvinen (Turku University Hospital), N.W. Pearlman (Denver VA Medical Center), J.P. Pignon (IGR), R.S. Rao (Tata Memorial Hospital, Bombay), J.M. Richard (IGR), K. Rufibach (Swiss Group for Clinical Cancer Research), F. Sanchiz (I Policlinico, Barcelona), H. Sancho-Garnier (Centre Val d'Aurelle), D.E. Schuller (Ohio State University Hospital, Columbus) V. Shanta (Madras Cancer Institute), R.J. Simes (NHMRC Clinical Trials Center, Camperdown), L. Smid (University of Ljubljana), L.A. Stewart (University of York), S. Staar (University of Cologne), P. Strojan (Institute of Oncology Ljubljana), H. Stuetzer (University of Cologne), H. Szpirglas (Centre Hospitalier Universitaire de la Pitié-Salpêtriére), G. Schwaab (IGR), N. Syz (IGR), S. Takaku (Saitama Medical School), S.G. Taylor (Rush Medical Center), J.S. Tobias (Cancer Research Campaign & University College London Cancer Trials Centre), R.J. Toohill (Medical College of Wisconsin), E.E. Vokes (University of Chicago Medical Center), P. Volling (University of Cologne), M.C. Weissler (University of North Carolina, Chapel Hill), T. Wendt (University of Jena), K.D. Wernecke (Charité University Hospital), J. Widder (University of Vienna), G.T. Wolf (University of Michigan), K. Yoshino (Osaka Medical Center for Cancer and Cardiovascular Disease).

Acknowledgements

The chief acknowledgement is to the trialists who agreed to share their data.

We also thank the following institutions for funding the investigators meeting or the meta-analysis project: Association pour la Recherche sur le Cancer (ARC No. 2015), Institut Gustave-Roussy, Ligue Nationale Contre le Cancer, Programme Hospitalier de Recherche Clinique (No. IDF 95009), Sanofi-Aventis.

We thank Denise Avenell, for secretarial assistance, Francine Courtial for electronic literature search, Charlotte Baey for the figures and Ana Chauvain for her contribution in editing the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2009.04.014.

References

[1] Ferlay F, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5. Version 2.0. Lyon: IARC Press; 2004.

[2] Pignon J-P, Bourhis J, Domenge C, Désigné L. On behalf of the MACH-NC Collaborative Group. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000;255:949–55.
[3] Baujat B, Mahé C, Pignon J-P, Hill C. A graphical method for exploring heterogeneity in meta-analysis: application to a meta-analysis of 65 trials. Stat Med 2002;21:2641–52.
[4] Pignon J-P, Le Maître A, Bourhis J, On behalf of the MACH-NC Collaborative Group. Meta-analyses of chemotherapy in head and neck cancer (MACH-NC): an update. Int J Radiat Oncol Biol Phys 2007;69:S112–4.
[5] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6.
[6] Yusuf S, Peto R, Lewis J, Collins R, Sleight T. Beta blockade during and after myocardial infarction: an overview of randomised clinical trials. Prog Cardiovasc Dis 1985;27:335–71.
[7] Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of randomized trials. N Engl J Med 1995;333:1444–55.
[8] Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 1995;311:899–909.
[9] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[10] Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 death among 75,000 women. Lancet 1992;339:1–15.
[11] Gabriele P, Orecchia R, Ragona R, et al. A cooperative AIRO/Piemonte randomized clinical trial of carboplatin as an adjunct to radiotherapy in head and neck cancer. Radiat Oncol 1994;32:S93.
[12] Bhowmik KT, Safaya A, Sharma R, Suri K, Bhatia JS, Das NI. Concomitant chemoradiotherapy in advanced head and neck cancers: Safdarjang hospital experience. Radiat Oncol 2001;58:S16.
[13] Haselow RE, Warshaw MG, Oken MM, et al. Radiation alone versus radiation with weekly low dose cisplatinum in unrescetable cancer of the head and neck. In: Fee Jr WE, Goepfert H, Johns ME, et al., editors. Head and neck cancer, vol. II. Philadelphia: BC Decker; 1990. p. 279–81.
[14] Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: an individual patient data meta-analysis of 15 randomized trials. Lancet 2006;368:843–54.
[15] Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/erbitux/Erbitux-H-558-II-05.pdf [last access on November 26, 2008].
[16] Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005;23:8636–45.
[17] Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705–15.
[18] Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695–704.
[19] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.

Articles

Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data

*J P Pignon, J Bourhis, C Domenge, L Designé, on behalf of the MACH-NC Collaborative Group**

Summary

Background Despite more than 70 randomised trials, the effect of chemotherapy on non-metastatic head and neck squamous-cell carcinoma remains uncertain. We did three meta-analyses of the impact of survival on chemotherapy added to locoregional treatment.

Methods We updated data on all patients in randomised trials between 1965 and 1993. We included patients with carcinoma of the oropharynx, oral cavity, larynx, or hypopharynx.

Findings The main meta-analysis of 63 trials (10 741 patients) of locoregional treatment with or without chemotherapy yielded a pooled hazard ratio of death of 0·90 (95% CI 0·85–0·94, p<0·0001), corresponding to an absolute survival benefit of 4% at 2 and 5 years in favour of chemotherapy. There was no significant benefit associated with adjuvant or neoadjuvant chemotherapy. Chemotherapy given concomitantly to radiotherapy gave significant benefits, but heterogeneity of the results prohibits firm conclusions. Meta-analysis of six trials (861 patients) comparing neoadjuvant chemotherapy plus radiotherapy with concomitant or alternating radiochemotherapy yielded a hazard ratio of 0·91 (0·79–1·06) in favour of concomitant or alternating radiochemotherapy. Three larynx-preservation trials (602 patients) compared radical surgery plus radiotherapy with neoadjuvant chemotherapy plus radiotherapy in responders or radical surgery and radiotherapy in non-responders. The hazard ratio of death in the chemotherapy arm as compared with the control arm was 1·19 (0·97–1·46).

Interpretation Because the main meta-analysis showed only a small significant survival benefit in favour of chemotherapy, the routine use of chemotherapy is debatable. For larynx preservation, the non-significant negative effect of chemotherapy in the organ-preservation strategy indicates that this procedure must remain investigational.

Lancet 2000; **355**: 949–55

*Collaborators listed at end of paper

Institut Gustav-Roussy, Villejuif, France (J P Pignon MD, J Bourhis MD, C Domenge MD, L Designé BSc)

Correspondence to: Dr J P Pignon, Department of Biostatistics and Epidemiology, Institut Gustav-Roussy, 39 rue Camille Desmoulins, 94 805 Villejuif cedex, France
(e-mail: jppignon@igr.fr)

Introduction

About 400 000 head and neck squamous-cell carcinomas are diagnosed worldwide annually,[1] most of which are locally advanced at presentation.[2] Surgery and/or radiotherapy are the mainstay of locoregional treatment,[3] and are often followed by chemotherapy especially in locally advanced disease. Chemotherapy induces tumour responses, but is toxic and costly. It is therefore important to know whether its addition leads to clinical benefits. Over 70 randomised trials in more than 12 000 patients have compared locoregional treatment plus chemotherapy versus the logoregional treatment alone. However, most of these trials were too small to detect even a moderate effect on survival. Yet chemotherapy is routinely used in locally advanced disease.[4] In the absence of a large (over 1000–2000 patients) randomised trial, the most reliable way to evaluate chemotherapy is to do a meta-analysis based on updated individual data. The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) collaborative group reports such an overview here.

Methods

The methods were specified in a protocol (available on request from JPP).

Eligibility criteria

Trials were eligible if previously untreated patients with non-metastatic head and neck squamous-cell carcinoma had been studied in one of these three comparisons: (1) the effect of chemotherapy—locoregional treatment was compared with locoregional treatment plus chemotherapy; (2) the timing of chemotherapy—neoadjuvant chemotherapy plus radiotherapy was compared with concomitant or alternating radiochemotherapy with the same drugs; and (3) larynx preservation with neoadjuvant chemotherapy—radical surgery plus radiotherapy was compared with neoadjuvant chemotherapy plus radiotherapy in responders or radical surgery and radiotherapy in non-responders.

Each trial had to be randomised such that investigators were unaware of the assigned treatment before deciding whether the patient was eligible. Trials were eligible if recruitment began after Jan 1, 1965, and ended before Dec 31, 1993, and if all randomised patients had undergone a potentially curative locoregional treatment and had not been treated for another cancer. Trials in tumours of the oral cavity, oropharynx, hypopharynx, and larynx were included. Trials including only nasopharyngeal carcinomas were excluded.

Identification of trials

Published and unpublished trials were included. Computerised searches of MEDLINE and Embase were supplemented with

Type of chemotherapy	Timing of chemotherapy			
	Adjuvant	Neoadjuvant	Concomitant	Total
Platin*+fluorouracil	1 (499)	15 (2487)	3 (517)	19 (3503)
Polychemotherapy with platin	1 (286)	10 (1364)	2 (87)	13 (1737)
Polychemotherapy without platin	1 (96)	4 (702)	4 (489)	9 (1287)
Monochemotherapy	5 (973)	2 (716)	17 (2634)	24 (4323)
Total	8 (1854)	31 (5269)	26 (3727)	65 (10850)†

*Cisplatin or carboplatin. †Two trials with three arms (control, neoadjuvant, and concomitant chemotherapy) were included both in neoadjuvant and concomitant comparisons and appear twice in table. Their control groups were therefore counted twice in analysis which thus was of 10 850 patients rather than 10 741.

Table 1: **Number of trials (patients) by type and timing of chemotherapy in meta-analysis comparing locoregional treatment with and without chemotherapy**

hand searches of meeting abstracts and references in review articles. Trial registers managed by the National Cancer Institute (PDQ, ClinProt) were consulted. Experts, pharmaceutical companies, and all trialists who took part in the meta-analysis were also asked to identify trials.

Data

The data collected for each patient were: age, sex, tumour site, tumour-node-metastasis classification or stage, histology, performance status, treatment allocated, and date of randomisation. The date and site of the first recurrence and second primary were also noted. Survival status and date of last follow-up were updated.

All data were checked for internal consistency and compared with the trial's protocol and published reports. Ranges were checked and extremes were verified with the trialists. Each trial was analysed individually and the survival analyses with trial data were sent to the trialists for review.

Analysis

Overall survival was the main endpoint. In the larynx-preservation meta-analysis, disease-free survival was the secondary endpoint and the events taken into account were local or distant recurrence, a secondary primary, and death.

For the main meta-analysis, trials were divided according to timing of chemotherapy: adjuvant, after the locoregional treatment; neoadjuvant, before the locoregional treatment, and concomitant, chemotherapy given concomitantly or alternating with radiotherapy. Trials were also grouped according to the type of chemotherapy: platin (cisplatin or carboplatin) plus fluorouracil, other platin-containing combinations, multiagent chemotherapy without platin, and single-agent chemotherapy (platin and others). All analyses were on an intent-to-treat basis.

Median follow-up was computed by the potential follow-up method.[5] Survival analyses were stratified by trial, and the log-rank observed minus expected number of deaths (O–E) and its variance were used to calculate individual and overall pooled hazard ratios with a fixed-effect model.[6] The weight of each trial in pooled analyses was proportional to the (O–E) variance which is approximately equal to one-fourth of the number of deaths. The absolute differences at 2 and 5 years were calculated with the baseline event rate in the control arm and the hazard ratio.[7] χ^2 tests were used to study heterogeneity. To study interaction between treatment and a covariate, an analysis stratified by trial was done for each covariate value, and hazard ratios for each value of the covariate were compared by a heterogeneity test. Non-stratified Kaplan-Meier survival curves are presented for the control and experimental groups. All p values are two-sided.

Results

The trials we included are detailed in *The Lancet*'s website with a short description of the excluded trials (http://www.thelancet.com) The trials' references and a sensitivity analyses can also be found there.

Trial category	Hazard ratio (95% CI)	Chemotherapy effect (p)	Heterogeneity (p)	Absolute benefit	
				At 2 years*	At 5 years*
Adjuvant	0·98 (0·85–1·19)	0·74	0·35	1%	1%
Neoadjuvant	0·95 (0·88–1·01)	0·10	0·38	2%	2%
Concomitant	0·81 (0·76–0·88)	<0·0001	<0·0001	7%	8%
Total	0·90 (0·85–0·94)	<0·0001	<0·0001	4%	4%

*Assuming survival rates of 50% at 2 years and 32% at 5 years in control groups.

Table 2: **Meta-analysis of locoregional treatment with and without chemotherapy: effect on survival**

Effect of chemotherapy on survival

The first meta-analysis included 63 trials (10 741 patients) that compared logoregional treatment with or without chemotherapy. Four trials (646 patients) were unpublished. We collected data for 463 of the 577 randomised patients excluded from the original published analyses. Follow-up was updated specifically for our meta-analysis in two-thirds of the trials, giving a median follow-up of 5·9 years. Trials are described here in table 1 and the patients in webtable 1.

There was a significant benefit (p<0·0001) for overall survival in favour of chemotherapy with a 10% reduction in the hazard ratio of death (95% CI 6–15% reduction, figure 1). This reduction corresponds to an absolute survival benefit of 4%, both at 2 years (from 50 to 54%) and 5 years (from 32 to 36%, figure 2). Heterogeneity was significant between trials (p<0·0001) and for chemotherapy timing (p=0·005).

In adjuvant trials, there was no significant effect of chemotherapy on survival and no heterogeneity between trials (table 2). In neoadjuvant trials, there was no heterogeneity between trials and no compelling evidence for an effect of chemotherapy on survival (table 2). There was, however, a significant benefit with platin plus fluorouracil (hazard ratio 0·88, 95% CI 0·79–0·97). The effect of this chemotherapy was significantly different (p=0·05) from that of the other regimens (1·01, 0·92–1·10).

In concomitant trials, there was a significant overall benefit of chemotherapy (table 2); however, considerable heterogeneity was found between these trials. To explore this heterogeneity we did further analyses. Trials were first divided according to locoregional treatment into a relatively homogeneous group of 12 trials (2516 patients) with conventional radiotherapy as locoregional treatment and the same dose in the two arms, and a second group of 14 heterogeneous trials (1211 patients). This second group of trials used various designs: surgery plus preoperative or postoperative radiotherapy with or without concomitant chemotherapy (five trials); a lower total dose of radiotherapy, or the same total dose delivered over a longer time, in the chemotherapy arm than that in the control arm, confounding the effect of chemotherapy with the effect of radiotherapy dose (seven trials); and chemotherapy alternated with radiotherapy (four trials including two also confounded). The hazard ratio of death in the first group of 12 trials (0·89, 0·81–0·97) was significantly different (test for interaction, p=0·0006) from that of the second group of 14 trials (0·67, 0·59–0·77). The heterogeneity in the concomitant group was mostly due to the second group of 14 trials (test for heterogeneity, p=0·0001).

The concomitant trials were also grouped according to the number of chemotherapy agents: single (17 trials,

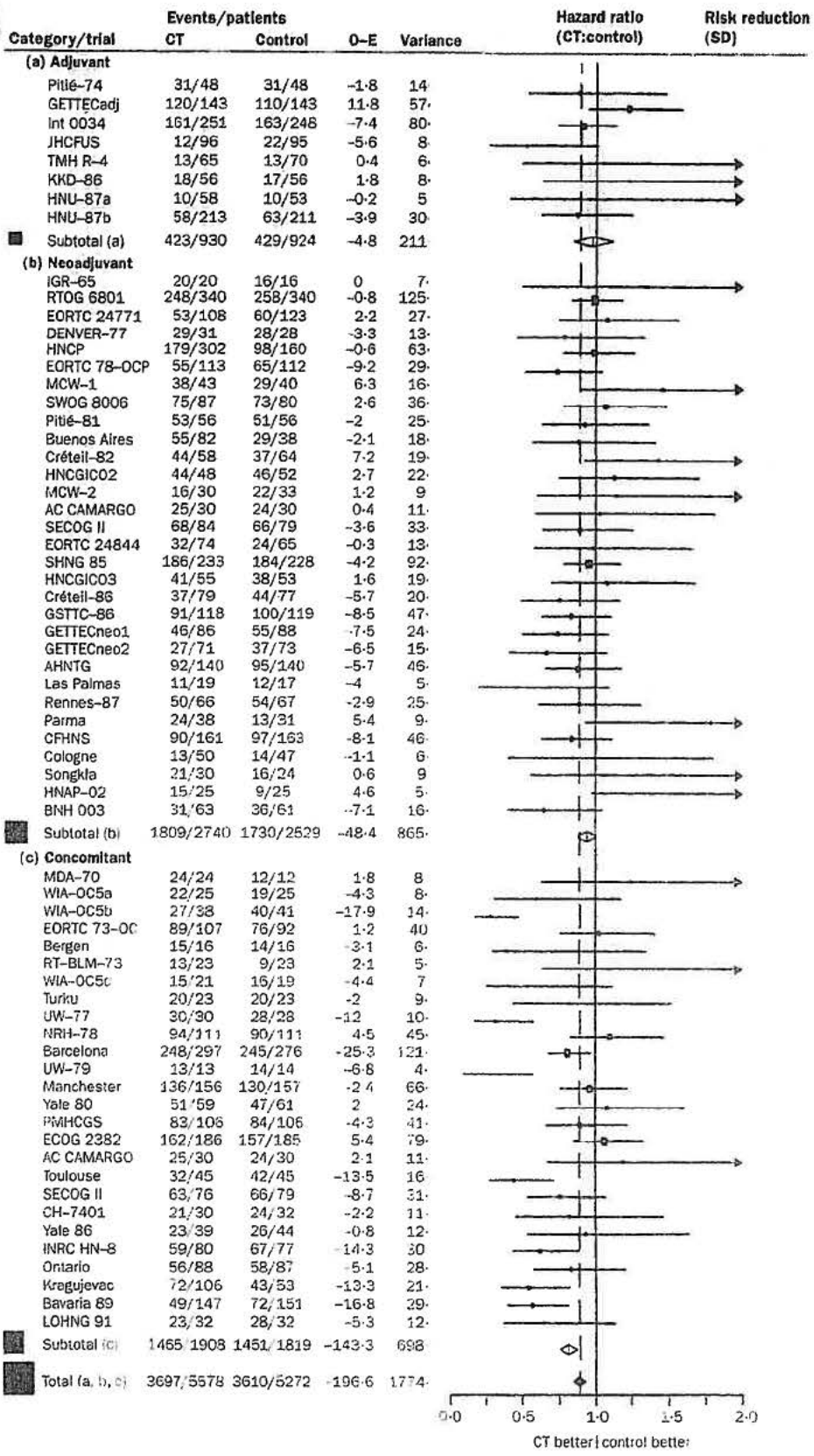
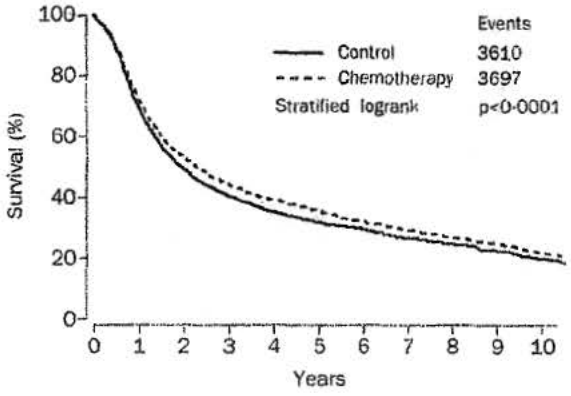


Figure 1: **Hazard ratio of death with locoregional treatment plus chemotherapy (CT) versus locoregional treatment alone**

Centre of each square is hazard ratio for individual trials and corresponding horizontal line is 95% CI; area of square is proportional to amount of information from trial. Broken line and centre of black diamond is overall pooled hazard ratio and horizontal tip of diamond is 95% CI. Open diamonds are hazard ratios of different timings of chemotherapy. Within timing, trials are ordered chronologically by date of start (oldest first). For each pooled hazard ratio, corresponding risk reduction (one minus hazard ratio) is given with its SD. Trial abbreviations are listed on website.



Number of patients

Control	5272	3530	2403	1793	1345	1005	740	553	412	308	235
Chemotherapy	5578	3913	2706	2106	1634	1218	881	649	470	367	271

Figure 2: **Survival in trials comparing locoregional treatment plus chemotherapy with locoregional treatment alone**

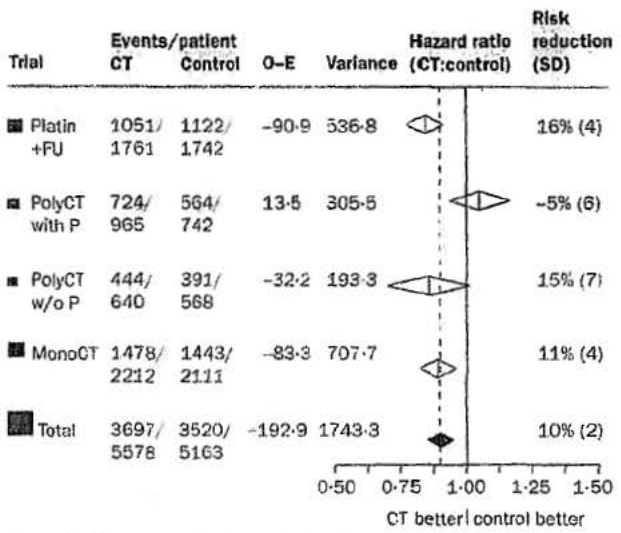


Figure 3: **Hazard ratio of death with locoregional treatment plus chemotherapy compared with locoregional treatment by types of chemotherapy**

Platin (cisplatin or carboplatin)+fluorouracil (FU), combination CT with platin (Poly CT+P), combination CT without platin (Poly CT w/o P), single-agent CT (mono CT) including platin. Test for heterogeneity between types of chemotherapy, p=0·02

2634 patients) versus multiple (nine trials, 1093 patients). This led to two heterogenous groups (tests for heterogeneity: p<0·0001 and p<0·01, respectively). The effect of concomitant chemotherapy was significantly (p<0·01) greater with multiagent chemotherapy than with single-agent chemotherapy (hazard ratio 0·69 *vs* 0·87).

In the overall group of trials, a non-significant increase in the risk of death was observed with multiagent chemotherapy containing a platin compared with controls, whereas a significant reduction in the risk of death was observed in the three other chemotherapy groups (figure 3).

For the effect of chemotherapy on survival by covariate values, the only significant observation was a decreasing effect of chemotherapy on survival with increasing age (trend test, p=0·05; figure 4).

Effect of timing of chemotherapy on survival

The second meta-analysis included six randomised trials that compared neoadjuvant with or without adjuvant chemotherapy plus radiotherapy versus concomitant or alternating radiochemotherapy. These trials included 861 patients who were older and had tumours at a higher stage than in the first meta-analysis (webtable 2). Median follow-up was 7·1 years (range 4·3–14·9). The pooled hazard ratio of death was 0·91 (0·79–1·06) in favour of alternating or concomitant radiochemotherapy, but this did not reach statistical significance (p=0·23, figure 5). This reduction in the risk of death translated into an absolute, but not statistically significant, survival benefit of 3%, both at 2 years (43 *vs* 40%) and 5 years (27 *vs* 24%). There was no significant heterogeneity between trials (p=0·16).

Larynx preservation

The third meta-analysis included patients with locally advanced laryngeal or hypopharyngeal carcinomas and compared radical surgery plus radiotherapy with a neoadjuvant combination of cisplatin and fluorouracil followed by radiotherapy in responders or radical surgery plus radiotherapy in non-responders. The three trials identified (table 3) included 602 patients, with a median follow-up of 5·7 years.

The pooled hazard ratio (1·19, 0·97–1·46, figure 6) showed a non-significant trend (p=0·1) in favour of the control group, corresponding to an absolute negative effect in the chemotherapy arm that reduced survival at 5 years by 6% (from 45 to 39%, figure 7). There was significant heterogeneity between the three trials (p=0·05). Adjustment for nodal status (N0/N1–3) or tumour subsite (glottic or subglottic *vs* supraglottic *vs* hypopharynx) led to similar results.

Trial	Inclusion period	Site	Stage	Randomisation	Drugs	Chemotherapy dose (mg/m²) × cycles	Locoregional treatment	Patients analysed/ randomised
VALCSG	1985–89	G 37%	III, IV	Arm 1	C F	100 × 2–3 5000 × 2–3	Radiotherapy (if PR) ± salvage surgery	332/332
		SG 63%		Arm 2	None	–	Total laryngectomy + postoperative radiotherapy	
GETTEC-IV	1986–89	G 59% SG 41%	III, IV	Arm 1	C F	100 × 2–3 5000 × 2–3	Radiotherapy (if PR) ± salvage surgery	68/68
				Arm 2	None		Total laryngectomy ± post operative radiotherapy	
EORTC 24891	1986–93	HP 78%	II to IV	Arm 1	C F	100 × 2–3 5000 × 2–3	Radiotherapy (if CR) ± salvage surgery	202/202
		LE 22%		Arm 2	None	–	Surgery + postoperative radiotherapy	

G=glottic/subglottic, SG=supraglottic, HP=hypopharynx, LE=lateral epilarynx, PR=partial response, CR=complete response. See website for trial abbreviations

Table 3: **Randomised trials comparing neoadjuvant combination of cisplatin (C) and fluorouracil (F) followed by radiotherapy in responders or by radical surgery plus radiotherapy in non-responders (arm 1) with radical surgery plus radiotherapy (arm 2)**

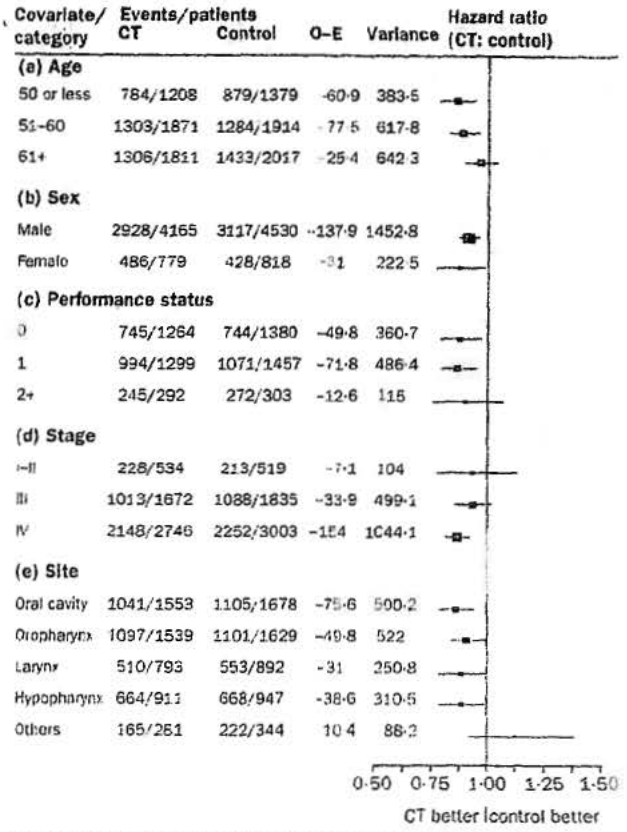


Figure 4: **Hazard ratio of death with locoregional treatment with or without chemotherapy by age, sex performance status, stage, or tumoural site.**
Test for trend for age was significant (p=0·05).

Types of first event were different in the two arms with twice as many locoregional recurrences, but less metastases, in the chemotherapy arm than in the controls. Rates of deaths unrelated to cancer were similar in both arms (table 4). The risk of recurrence, second, primary, or death was non-significantly (p=0·1) higher in the chemotherapy group than in the control group (hazard ratio 1·18, 0·97–1·44), which corresponds to a reduction in disease-free survival at 5 years from 40% in the controls to 34% in the chemotherapy arm. There was significant overall heterogeneity between the trials (p=0·04), most of which was accounted for by heterogeneity between tumour sites (p=0·03) with some suggestion that the effect of chemotherapy was negative (hazard ratio 1·4) for larynx tumours but may be beneficial (0·9) for hypopharyngeal tumours. The proportion of patients alive at 5 years was 45% in the control arm and 39% in the chemotherapy arm (23% of the patients with their larynx and 16% without).

	Chemotherapy (n=305)	Control (n=297)
Type of first event		
Recurrence or secondary primary*	51%	46%
Locoregional recurrence	25%	12%
Metastasis	14%	19%
Locoregional recurrence and metastasis	3%	3%
Second primary	9%	12%
Death without recurrence or second primary	19%	16%
Total proportion of events	70%	62%
Alive without recurrence or second primary	30%	38%

*Distribution of type of events was significantly different between arms (p=0·001).

Table 4: **Larynx preservation: patients' status for disease-free survival**

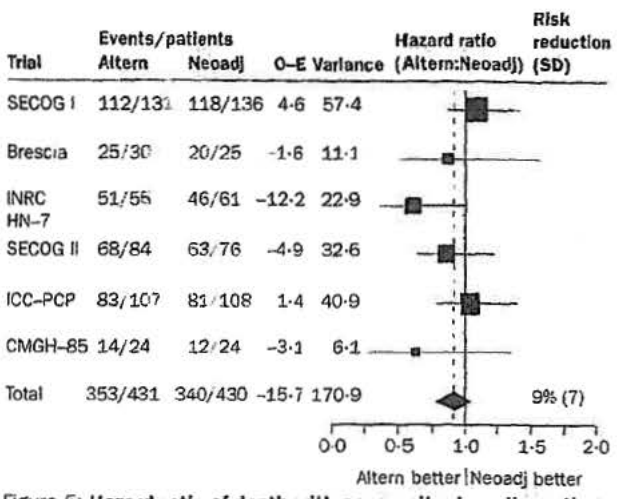


Figure 5: **Hazard ratio of death with concomitant or alternating radiochemotherapy compared with neoadjuvant chemotherapy plus radiotherapy with same drugs in both arms**
Overall hazard ratio 0·91 (95% CI 0·79–1·06), p=0·23. Test for heterogeneity, p=0·16. Altern=alternating, Neoadj=neoadjuvant.

Discussion

In the first meta-analysis on the addition of chemotherapy to locoregional treatment, the most important result was a small, but statistically significant, overall benefit in survival with chemotherapy (the absolute benefit at 2 and 5 years was 4%). This size of effect of chemotherapy in head and neck squamous-cell carcinoma is similar to that observed in non-small-cell lung cancer.[11] Prespecified analyses of the timing of chemotherapy suggested no significant benefit of adjuvant or neoadjuvant chemotherapy but a significant benefit of concomitant chemotherapy (absolute benefit at 2 and 5 years of 8%). The benefit within the concomitant group came from 14 very heterogenous trials which included only 11% of the patients; thus, the size of the benefit remains uncertain. A sensitivity analysis (see website) showed the robustness of the overall results and confirmed the uncertainty of the results in the concomitant group. At the MACH-NC investigators' meeting (January, 1997), we identified 18 trials, in progress or closed since 1994 and expected to

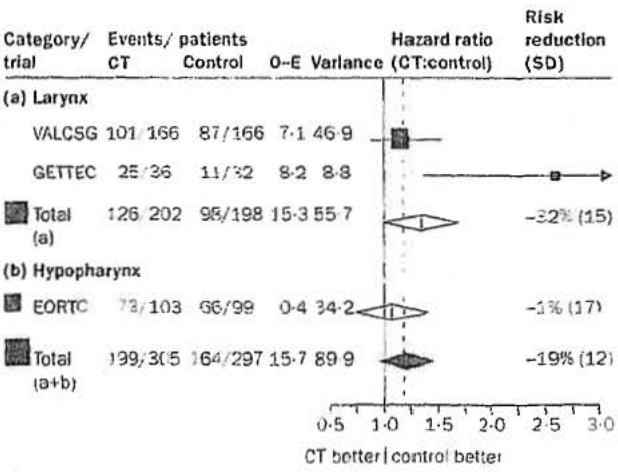
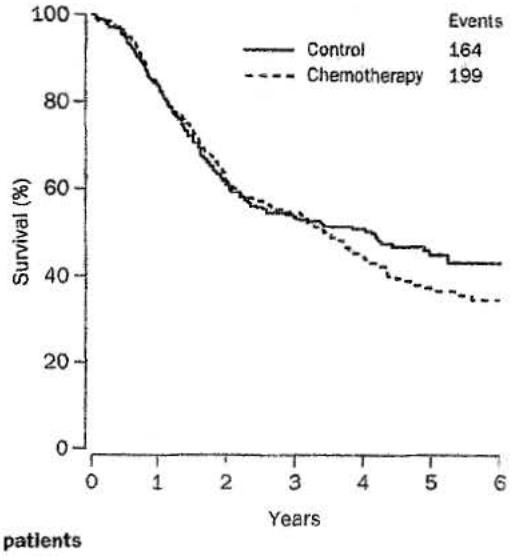


Figure 6: **Hazard ratio of death of neoadjuvant cisplatin-fluorouracil followed by radiotherapy in responders or by radical surgery plus radiotherapy in non-responders compared with radical surgery plus radiotherapy**
Overall hazard ratio 1·19 (95% CI 0·97–1·46), p=0·10. Test for heterogeneity, p=0·05.



Number of patients

Control	297	251	188	161	119	86	56
Chemotherapy	305	258	199	165	117	77	54

Figure 7: **Survival in trials comparing radical surgery plus radiotherapy with neoadjuvant combination of cisplatin-fluorouracil followed by radiotherapy in responders or by radical surgery plus radiotherapy in non-responders**
Difference between survival curves was not significant (stratified logrank p=0·10).

accrue approximately 5000 patients. Chemotherapy was generally given with radiotherapy; only two trials had an alternating radiochemotherapy arm. The results of these 18 trials will further define the benefits of concomitant radiochemotherapy and identify chemotherapy regimens for general use.

The suggestion of a decreasing effect of chemotherapy with increasing age (trend test p=0·05) might be partly explained by lower compliance and higher toxicity rates in older patients (data not shown). Individual data from 10 741 patients randomised in 63 trials were collected (compared with 7443 patients in the largest meta-analysis of data extracted from trial publications[12]), but data from some old trials on 898 patients were not available. Data on locoregional and distant recurrences were collected but were incomplete.

In the second meta-analysis on neoadjuvant and concomitant chemotherapy, we found a non-significant survival benefit in favour of the concomitant group (hazard ratio 0·91). This finding agrees with the results of the main meta-analysis, which only indirectly estimated the hazard ratio of death with concomitant versus neoadjuvant chemotherapy. The "indirect" hazard ratio of 0·85 was in the range of the 95% CI of the "direct" hazard ratio (0·79–1·06). Thus both direct and indirect comparisons of neoadjuvant and concomitant (or alternating) chemotherapy were consistent with a benefit for the concomitant modality.

In the third meta-analysis on larynx preservation, we cannot exclude a negative impact of this strategy on survival and disease-free survival. Analysis by tumour site showed that this negative impact may be limited to the larynx and not apply to tumours originating in the hypopharynx. The difference in response criteria between the hypopharynx trial (complete response) and the two larynx trials (partial or complete response) may account for the discrepant results between the two types of trials. Future trials should be designed with adequate power to evaluate treatment effect by site and subsite (ie, glottic larynx, supraglottic larynx, pyriform sinus). The hazard ratio of death observed in this comparison (1·19) was significantly different (p<0·01) from the hazard ratio (0·88) from the meta-analysis that compared locoregional treatment plus neoadjuvant platin and fluorouracil to the same locoregional treatment. Moreover, the difference in disease-free survival (table 3) was due to a higher rate of locoregional failure in the patients who received neoadjuvant chemotherapy, which suggests that chemotherapy as a single modality before radiotherapy is an inadequate substitute for surgery. The results should be balanced against the fact that 23% of the patients were alive at 5 years with a preserved larynx.

Our meta-analyses used individual patients' data,[13] with intent-to-treat analysis, updated follow-up, survival analyses, and covariates. Clinical heterogeneity between trials was large in populations included (eg, site of tumour) and design (locoregional treatment, drugs, timing) which makes a simple conclusion difficult. Nevertheless, we think that our study represents the best available evidence on the role of chemotherapy in head and neck carcinoma.

In conclusion, there was a small statistically significant benefit on survival when chemotherapy was added to a locoregional treatment in patients with non-metastatic head and neck squamous-cell carcinoma. However, given such a small benefit, the routine use of chemotherapy remains debatable and it will be important in future trials to evaluate morbidity, quality of life, and cost-benefit. The overall benefit was mainly due to the favourable effect of concomitant/alternating radiochemotherapy. However, the concomitant trials were highly heterogenous, which makes a conclusion difficult. In addition, no standard concomitant radiochemotherapy regimen has been defined. Future research should focus on this group of treatments. Neither adjuvant chemotherapy nor neoadjuvant chemotherapy provided significant benefit; therefore these modalities should not be used outside clinical trials. In the larynx preservation meta-analysis, we saw a non-significant negative effect of chemotherapy (used to avoid radical surgery), which indicates that larynx preservation should remain investigational.

MACH-NC Collaborative Group
Writing committee—J P Pignon, J Bourhis, C Domenge, C Hill.
Trialists—D J Adelstein (Cleveland Clinic Foundation, Cleveland, USA); J M Bachaud (Institut Claudius Regaud, Toulouse, France); W R Bezwoda (University of Witwatersrand, Johannesburg, South Africa); A Buffoli (Instituto di Radioterapie Oncologica, Udine, Italy); G P Browman (McMaster University, Hamilton, Canada); B H Campbell (Medical College of Wisconsin, Milwaukee, USA); A Carugati (Instituto de Oncologia A H Roffo, Buenos Aires, Argentina); J R Clark (Dana -Farber Metro West Cancer Center, Framingham, USA); L Collette (European Organization for Research and Treatment of Cancer, Brussels, Belgium); O Dal Canton (Ospedale S Giovanni Vecchio, Torino, Italy); D Dalley (St Vincent's Hospital, Sydney, Australia); J Depont (Hôpital Bichat, Paris, France); A Deszcz-Thomas (Hôpital de la Pité-Salpêtrière, Paris); B Di Blasio (Azienda Ospedaliera, Parma, Italy); C Domenge (Institut Gustave-Roussy, Villejuif, France); J F Evensen (Norwegian Radium Hospital, Oslo, Norway). J J Fischer (Yale University, New Haven, USA); D Gedouin (Centre Eugène Marquis, Rennes, France); F Geara (MD Anderson Cancer Center, Houston, USA); N K Gupta (Christie Hospital, Manchester, England); E Haddad (Hôpital Henri Mondor, Créteil, France); B G Haffty (Yale University); Y Hasegawa (Aichi Cancer Center Hospital, Nagaya, Japan); M Horiuchi (Tokai University, Isehara, Japan); J Houghton (CRC Clinical Trials Center, London, England); B Jeremic (KBC Kragujevac, Kragujevac, Yugoslavia); T Jouffroy (Institut Curie, Paris); A Jortay (CHU Brugmann, Brussels, Belgium); B Kapstad (University of Bergen,

Bergen, Norway); L P Kowalski (A C Camargo Hospital, Sao Paulo, Brazil); S Kramer (Thomas Jefferson University Hospital, Philadelphia, USA); K S Krishnamurthi (Cancer Institute [WIA], Chennai, India); G Laramore (University of Washington Medical Center, Seattle, USA); J L Lefebvre (Centre Oscar Lambret, Lille, France); T Leong (Eastern Cooperative Oncology Group, Boston, USA); F Lewin (Huddinge University Hospital, Stockholm, Sweden); B Luboinski (Institut Gustave-Roussy); T Maipang (Prince of Songkla University, Songkla, Thailand); M Martin (Centre Hospitalier Inter Communal, Créteil, France); J J Mazeron (Hôpital de la Pité-Salpêtrière); M Merlano (Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy); S Metha (Ashok Nagar Society, Bombay, India); K Morita (Aichi Cancer Center); V Mosseri (Institut Curie); A Murias (Hospital Insular de Gran Canaria, Las Palmas, Spain); G Numico (Istituto Nazionale per la Ricerca sul Cancro, Genova); B O'Sullivan (Princess Margaret Hospital, University of Toronto, Canada); A Paccagnella (General Hospital, Padova, Italy); T Pajak (Radiotherapy Therapy Oncology Group, Philadelphia, USA); L M Parvinen (Turku University Hospital, Turku, Finland); N W Pearlman (University of Colorado, Denver, USA); R S Rao (Tata Memorial Hospital, Bombay, India); J M Richard (Institut Gustave-Roussy); F Sanchiz (Centre de Radioterapia i Oncologica, Barcelona, Spain); H Sancho-Garnier (Centre Val d'Aurelle, Montpellier, France); D E Schuller (Arthur G James Cancer Center & Richard J Solove Research Institute, Colombus, USA); V Shanta (Cancer Institute [WIA]); L Smid (University of Ljubljana, Ljubljana, Slovenia); H Szpirglas (Hôpital de la Pité-Salpêtière); G Schwaab (Institut Gustave-Roussy); S G Taylor (Rush Medical Center, Chicago, USA); S Takaku (Saitama Medical School, Saitama, Japan); J S Tobias (Middlesex Hospital, London, England); R J Toohill (Medical College of Wisconsin); P Volling (University Hospital, Cologne, Germany); MC Weissler (University of North Carolina, Chapel Hill, USA); T Wendt (Friedrich Schiller Universitat, Jena, Germany); G T Wolf (University of Michigan Hospital, Ann Arbor, USA); K Yoshino (Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan).

Secretariat—J P Armand, J Bourhis, L Designé, C Domenge, S Guérin, C Hill, P Jan, B Luboinski, M Luboinski, J P Pignon (Institut Gustave-Roussy); J L Lefevbre (Centre Oscar Lambret); H Sancho-Garnier (Centre Val d'Aurelle, Montpellier, France).

Steering committee—Chair: A A Forastiere (John Hopkins Oncology Center, Baltimore, USA). Members: H G Bartelink (Netherlands Cancer Institute, Amsterdam, Netherlands); F Eschwege (Institut Gustave-Roussy); K K Fu (University of California, San Francisco, USA); F Lewin (Karolinska Hospital, Stockholm, Sweden); R Molinari (Istituto Nazionale Tumori, Milano, Italy); M Merlano (Istituto Nazionale per la Ricerca sul Cancro, Genova); R J Simes (NHMRC Clinical Trials Center, Camperdown, Australia); L A Stewart (MRC Cancer Trial Office, London, UK); E E Vokes (University of Chicago Medical Center, Chicago, USA); G T Wolf (University of Michigan Hospital).

Acknowledgments

Our main acknowledgment is to the trialists who agreed to share their data.

We also thank the following institutions and organisations for funding the investigators' meeting or the meta-analysis project: Association pour la Recherche Médicale (ARC 6560), Banque Nationale de Paris, Bristol-Myers Squibb France and Europe, European Commission (Biomed 2 961321), Fondation pour la Recherche Médicale, Institut Gustave-Roussy, Glaxo France, Institut Nationale de la Santé et de la Recherche Médicale, Ligue Nationale Contre le Cancer, Programme Hospitalier de Recherche Clinique (IDF 95013), Servier Medical, University Paris XI, and Smith-Kline-Beecham.

We thank Stéphanie Bertin, Serge Koscielny, Rémi Lancar, Lydia Nikasinovic, and Diane Potvin who contributed to the computing and data management. We thank Denise Avenell, Sylviane Iacobelli, Dalila Zeddoun, and Christiane Musso for secretarial assistance, Francine Courtial for electronic literature searching, and Lorna Saint-Ange for co-editing the manuscript. This report will be included in the Cochrane Review Group on Ear, Nose and Throat Disorders.

References

1 Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. Cancer incidence in five continents. Vol 6. Lyon: IARC, 1992.

2 Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1996. *CA Cancer J Clin* 1996; **65**: 5–27.

3 Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med* 1993; **328**: 184–94.

4 Hahari P. Why has induction chemotherapy for advanced head and neck cancer become a United States community standard of practice? *J Clin Oncol* 1997; **15**: 2050–55.

5 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Controlled Clin Trials* 1996; **17**: 343–46.

6 Yusuf S, Peto R, Lewis J, Collins R, Sleight T. Beta blockade during and after myocardial infarction: an overview of randomised clinical trials. *Prog Cardiovasc Dis* 1985; **27**: 335–71.

7 Stewart LA, Parmar MKB. Meta-analysis of the literature or individual patient data: is there a difference? *Lancet* 1993; **341**: 418–22.

8 The Department of Veteran Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991; **324**: 1685–90.

9 Richard JM, Sancho-Garnier H, Pessey JJ, et al. Randomized trial of induction chemotherapy in larynx carcinoma. *Eur J Cancer* 1998; **34**: 224–28.

10 Lefebvre JL, Chevalier D, Luboinski B, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. *J Natl Cancer Inst* 1996; **88**: 890–99.

11 Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 1995; **311**: 899–909.

12 Bourhis J, Pignon JP. Meta-analyses in head and neck squamous cell carcinoma: what is the role of chemotherapy? *Hematol Oncol Clin North Am* 1999; **13**: 769–75.

13 Oxman AD, Clarke MJ, Stewart LA. From science to practice: meta-analyses using individual patient data are needed. *JAMA* 1995; **274**: 845–46.

References 70 and 71 (see website) have W R Bezwoda as a co-author. One of Dr Bezwoda's other studies has recently been audited negatively. References 70 and 71 contributed 58 and 27 patients to the meta-analysis. The authors have informed us that the overall hazard ratio in the meta-analysis is the same with or without these data. In the concomitant group, the hazard ratio changes from 0·81 to 0·83, but is anyway not statistically significant—Ed L.

Cancer Treatment Reviews (1985) **12** (*Supplement A*), 111 124

Carboplatin as a potentiator of radiation therapy

Evan B. Douple, Robert C. Richmond, Julia A. O'Hara and Christopher T. Coughlin

Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Hanover, N.H. 03756, U.S.A.

A rationale for coordinating the administration of carboplatin with radiation to achieve enhancement of cancer therapy is developed. This approach is based upon a review of the reports of effects in a variety of systems, effects attributed to interactions between cisplatin or other platinum analogs and radiation. Two major effects include radiosensitization (RS) of hypoxic cells with platinum present during irradiation and potentiation of cell kill with platinum complexes administered after irradiation. Both these effects are expected to result in an improved therapeutic ratio. The latter effect may include inhibition of recovery from radiation-induced potentially lethal damage (PLD) and sublethal damage (SLD). Evidence for RS by carboplatin with an enhancement ratio (ER) of 1.8 is presented in Chinese hamster lung cells (V79) irradiated in culture under hypoxic conditions. Potentiation of radiation therapy in mice bearing a transplanted mouse mammary tumor (MTG-B) is reported as a supra-additive tumor growth delay when 60 mg/kg carboplatin is administered either 30 minutes before or immediately after 20 Gy of X-irradiation. Improved efficacy resulting from ongoing clinical trials coordinating cisplatin with radiation should support the role for carboplatin as a potentiator of radiation therapy since this second generation complex of platinum also interacts with radiation and larger concentrations of platinum should be attainable in tumors using the new drug.

The rationale for potentiation of radiation therapy

Potentiation of radiation-induced killing by cisplatin in hypoxic bacterial spores was reported nearly a decade ago by Richmond & Powers (1). Preclinical trials in cultured cells and animal tumors (for review see 2–4) have established a rationale for combining cisplatin with radiation. Clinical trials have commenced intending to exploit the potential interactions between this parent platinum coordination complex and radiation (5, 6). Preliminary results of these clinical trials which combine cisplatin with radiation have been encouraging. However, it would be very fortuitous if the current experimental protocols represent the optimum time, dose and sequence relationships for the combined modality approach to cancer therapy. The elucidation of such optimal protocol designs with the potential for enhanced therapeutic efficacy will depend upon the acquisition of additional knowledge of mechanisms from preclinical studies.

Reprint requests to: Evan B. Douple, Radiobiology Laboratories, Norris Cotton Cancer Center, Hanover, NH, 03756, USA.

0305–7372/85/12A0111+14 $03.00/0

While these experiments are in progress, additional information is emerging on three fronts with promise for further enhancement of radiation therapy. First, new methods for the delivery of higher cisplatin doses have been introduced clinically (7) with an assumed attendant increase in intratumor platinum concentrations providing more of an appropriate, but unknown, platinum species for interaction. Second, the introduction of a new generation of platinum complexes as chemotherapeutic agents, principally carboplatin (CBDCA) (8) and iproplatin (CHIP) (9), has made available complexes with improved therapeutic indices. Several of the platinum complexes have exhibited interactions with radiation in bacterial systems (10, 11) and in cultured mammalian cells (12, 13). It is hoped that some of these may prove to be more proficient at enhancing effects of radiation therapy. Third, new platinum complexes may be designed and synthesized to exploit the targeting concept of delivering platinum to important biomolecules (11, 14) or to incorporate chemical structures known to be radiosensitizers (11, 15, 16).

The goal of combining chemotherapy with radiation to improve local tumor control is to potentiate cell kill without increasing normal tissue injury, thereby improving the therapeutic ratio. The results of preclinical studies have indicated that cisplatin may interact with radiation producing at least two distinct effects which might result in an improvement in the therapeutic ratio. The first of these effects is radiosensitization of hypoxic cells (see Fig. 1), and the second is potentiation of cell kill if cisplatin is administered after irradiation at a time when free radical-based radiosensitization mechanisms (17) are not involved. This second effect (see Fig. 2) is demonstrated in experiments which produce enhanced cell survival when confluent cultures of mammalian cells are incubated post-irradiation for a few hours prior to subculturing for viability assay by colony forming units. The increased survival is defined operationally as the recovery from radiation-induced potentially lethal damage (PLD). The reduction in this survival when platinum complexes are added immediately following irradiation may reflect an

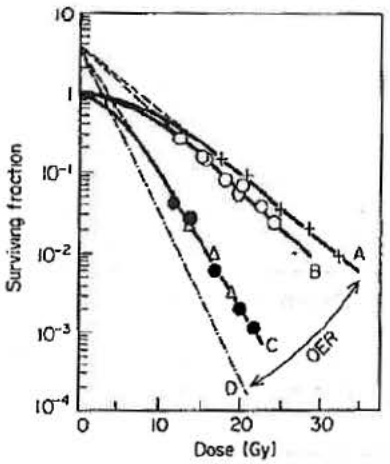


Figure 1. Radiosensitization of hypoxic V79 cells by 5 μM cisplatin (open circles; $D_0 = 4.74$ Gy; ER = 1.15) compared to 1 mM misonidazole (closed circles; $D_0 = 2.87$ Gy; ER = 1.9). A is hypoxic without drug curve ($D_0 = 5.45$ Gy). D is a theoretical air curve ($D_0 = 1.82$ Gy) for an RBE of 3.0 which would not be expected to be modified significantly by the addition of misonidazole or cisplatin. Open triangles result when a smaller concentration of misonidazole (0.2 mM) is combined with cisplatin producing an enhancement greater than expected from the sum of the two agents acting alone with radiation. Data redrawn from Stratford *et al.* (19) with permission of publisher.

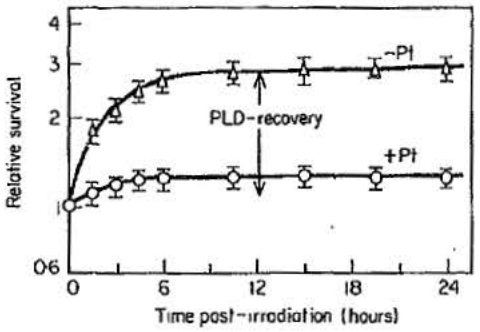


Figure 2. Potentiation of rat hepatoma cells (H4) by 2.5 μM cisplatin present during the post-irradiation incubation prior to assay for viability, suggesting inhibition of PLD recovery. Relative survival of plateau phase cells irradiated with 750 rad after incubation for different time lengths in MEM (open triangles) or in the presence of cisplatin (open circles). Results have been corrected for drug toxicity. Data redrawn from Carde and Laval (20) with permission of publisher.

inhibition of PLD recovery (20–22), although other possible mechanisms have been proposed (6, 22). Inhibition of recovery from sub-lethal damage (SLD) by cisplatin is also documented (20, 21).

Radiosensitization

The two experimental conditions previously cited, cells deficient in oxygen (hypoxic) as well as density-inhibited, nutritionally depleted plateau-phase cells capable of recovery from PLD, may represent conditions particular to tumors. These conditions would be expected to confer radioresistance to the tumor cells. First, radiation-induced inhibition of mitotic activity results in a steeper killing curve if oxygen is present as illustrated in Figure 1. The D_0 values i.e., the inverse of survival curve slopes, for the aerated and hypoxic curves differ by approximately 3.0. This enhancement ratio (ER) due to the presence of oxygen is called the oxygen enhancement ratio (OER). Tumors are expected to contain a significant population of viable hypoxic cells, since oxygen is consumed before it penetrates distances greater than about 100 microns from blood vessels (23). For decades intensive radiation oncology research efforts have been directed to overcome this radioresistance of tumor cells which might be responsible for certain cancer treatment failures. One approach to this problem has been to identify chemicals which are oxidizing agents that operate as radiosensitizers of hypoxic cells through short lived free radical chemical events that occur during irradiation. A therapeutic gain might be expected if hypoxic cells in tumors are radiosensitized by an agent present during irradiation without any enhancing effect on aerated cells, assuming that most normal cells are well oxygenated. Classes of electron affinic agents such as the nitroimidazoles have been identified, and some of these compounds are undergoing clinical trials as radiosensitizers (for review see 24).

Early bacterial studies reported significant radiosensitization by cisplatin preferential to the hypoxic cell and required concentrations of only 10–50 μM (1, 10, 25). Cisplatin produced relatively small ER values in Chinese hamster lung cells (V79), approximately 1.15 for 5 μM concentrations (19) and about 1.3 at concentrations of 10 μM (12). Only 2.5 μM cisplatin produced an ER of 1.25 in rat hepatoma cells (H4) (20). It is difficult to test

for this supra-additive interaction using higher concentrations of cisplatin since the cytotoxicity from the platinum alone becomes severe. However, results of preliminary experiments suggest that the effects become larger at higher concentrations (E. B. Douple, unpublished data). ER values as high as 1.9 were reported when hypoxic Chinese hamster ovary (CHO) cells were irradiated following certain time periods and specific concentrations of iproplatin (26). However, under other conditions potentiation of radiation-induced cell kill was reported for well-oxygenated CHO cells. Probably the largest ER values for platinum complexes in mammalian cells reported to date (ER = 2.4) were obtained using FLAP, a platinum complex which includes two electron affinic 5-nitroimidazole metronidazole moieties attached to dichloroplatinum (15).

Evidence for potentiation of radiation therapy by cisplatin in animal tumor systems has been reported in several studies (27–34) and the enhanced tumoricidal effects apparently represent a therapeutic gain since they have not been accompanied by an equivalent enhancement of normal tissue damage. An ER value of 1.7 was reported for combinations of single doses of 6 mg/kg cisplatin injected 30 minutes before irradiation using tumor cure as an assay endpoint in a transplantable mammary tumor system (27). The same drug treatment immediately after irradiation produced some potentiation (1.2–1.3) and no interaction was observed in irradiated skin surrounding the tumor in both of these regimens. Since conventional clinical radiotherapy is delivered in multiple treatment fractions, mouse tumors (RIF-1) were treated with 5 daily fractions of cisplatin (2.4 mg/kg/day) immediately before each of 5 daily X-ray doses of 4 Gy (29). In these experiments ER values of 1.9 were computed (P. Levlieveld and H. Bartelink, personal communication), and cisplatin was one of only two drugs which produced supra-additivity. This X-ray enhancement is dependent upon the timing of the drug to the radiation therapy.

Potentiation of radiation therapy: PLD recovery inhibition

The role of PLD recovery in clinical radiocurability is still uncertain, but the phenomenon has received considerable attention recently since Weichselbaum and colleagues have correlated the radioresistance (or poor radiocurability) of some human solid tumors with a high proficiency for PLD recovery (35–39). This recovery is significant in cultured melanoma cells after radiation doses relevant to those used in clinical radiotherapy (37, 38). Hypoxic, radioresistant tumor cells are likely to be in a deficient nutrient and metabolic state conducive to the plateau phase and optimal PLD recovery (40, 41). Cisplatin appears to inhibit PLD recovery when administered to cultured V79 cells (21) and H4 rat hepatoma cells (20) at doses less than those required for radiosensitization of hypoxic cells. This effect resulting from the presence of platinum after irradiation, at a time when free radical-mediated radiosensitization does not occur, has been reported for cisplatin in CHO cells (42) and for other platinum analogs (22, 26). One of these studies (26) used a 3 Gy radiation dose which approaches the clinical range, while a second study (22) reported an enhanced cell kill which exceeded that expected from total inhibition of PLD recovery. In this latter report the authors proposed that a potentiation of cell kill might result from an enhanced chemotoxicity in cells which have been exposed to radiation.

Although we do not know whether either or both of these mechanisms are operational in

tumors treated with the combined platinum and radiation therapy, the potentiation observed in animal studies (27–34) may result from either or both of these effects since platinum administered before radiation would also be present during the post-irradiation interval. Furthermore, the initial encouraging preliminary results of clinical trials (5, 43–50) may be an indication that these effects are operating in human tumors. It has been suggested that enhanced therapeutic effects at levels of cisplatin present when patients are irradiated most likely reflect post-irradiation interactions rather than radiosensitization of hypoxic cells (5). A summary of events which have led to the development of a clinical rationale for combining platinum chemotherapy with radiation is presented in Figure 3.

Role of carboplatin in combination with radiation

As described elsewhere in this volume, carboplatin has emerged as a promising new second generation platinum complex on the merits of results of clinical trials (8, 53–55). Since carboplatin is less toxic than cisplatin and not limited by nephrotoxicity or gastrointestinal toxicities (53), higher levels of platinum may be administered to patients (53–55) and mice (56) with the attainment of higher peak plasma levels (55, 56) and the potential for higher platinum levels in solid tumors (5, 11, 57, 58) relative to cisplatin. However, few studies have compared the potentiation of radiation by carboplatin with that produced by cisplatin.

Richmond *et al.* (11) reported significant radiation potentiation in hypoxic *S. typhimurium* cells by 200 μM carboplatin as illustrated in Figure 4. This study also reported an increased toxicity of carboplatin if the drug is irradiated under N_2-gassed conditions prior to administration to toxic cells. The mechanism for this radiation-induced formation of toxic platinum products is not known, but it is hypothesized that the mechanism involves the free radical formation and subsequent reaction of Pt (I) intermediates in ways analogous to that described for cisplatin (59). The observed hypoxic radiosensitization by carboplatin is greater than can be accounted for by the post-irradiation toxicity of the carboplatin during radiation. An unirradiated 200 μM carboplatin solution is nontoxic to these cells for up to 90 minutes for the conditions of these experiments. The oxidation and reduction of a limited number of platinum complexes have been studied (59, 60) although relationships between characteristics such as reduction potentials and efficacy for radiosensitization have not been established at this time. It has been established that the free solution compartment, i.e. platinum complexes not bound to biomolecules, is important for hypoxic bacterial cell radiosensitization (10, 18, 25). It is hypothesized that the free solution compartment may also apply to mammalian cell radiosensitization (5, 11). This hypothesis would predict that the use of less toxic analogs such as carboplatin at higher concentrations might provide more free solution platinum for interaction with radiation.

Carboplatin has been observed to be an hypoxic cell radiosensitizer in V79 cells (61) and CHO cells (R. C. Richmond, unpublished data). In the former study, a 100 μM carboplatin dose at 37°C for 1 hour produced a small ER of 1.1. In the latter study, a 200 μM carboplatin dose at 37°C for 30 minutes followed by a 30 minute degassing and irradiation at room temperature produced a five-fold increase in hypoxic cell killing at the 3×10^{-2} radiation-induced survival level but was without effect on oxic cells.

Experiments were performed in our laboratory to evaluate this effect. For these experiments stock cultures of V79 were trypsinized and single cell suspensions were

1971	Phase I clinical trials of cisplatin begun	
1974	RT and cisplatin synergism for P388 therapy in mice (52)	
1976	Potentiation of RT in mammalian cells by a Pt complex (26)	Radiosensitization of bacterial spore by cisplatin (1)
1977	Therapeutic potentiation of rodent tumors by cisplatin and radiation (34)	Radiosensitization of *E. coli* and effects on cell DNA by cisplatin (25)
1978	Radiation chemistry of cisplatin and effects on DNA (59)	Radiosensitization of hypoxic mammalian cells by cisplatin and other complexes (12)
1979	Inhibition of recovery from radiation-induced SLD and PLD by cisplatin (21) Clinical trial using cisplatin plus radiation (76)	Effects of radiation and cisplatin on normal tissues (65–67, 79)
1980	Enhancement by cisplatin plus misonidazole (19)	
1981	ER in mouse mammary tumor by cisplatin before and after irradiation (27)	
1982	Phase I clinical trials of carboplatin encouraging (8) Enhanced chemotoxicity (EC) by platinum complex after irradiation (22)	Electron affinic moiety attached to Pt for radiosensitization (15)
1983	Phase I clinical trials of iproplatin encouraging (9) Platinum levels in solid tumors greater at 6 hrs compared to earlier or later time periods (71)	Potentiation by low dose rate RT plus cisplatin in mouse tumor (30)
1984	Radiation-enhanced toxicity of Pt complexes in bacteria (10,11)	
1985	Radiation chemistry of cisplatin and additional platinum complexes (60) Clinical trials testing combined carboplatin plus radiation	Histological evidence for cisplatin-radiation interaction in the local control of clinical tumors (5)

Figure 3. Some events leading to the development of rationale for combined platinum-radiation therapy.

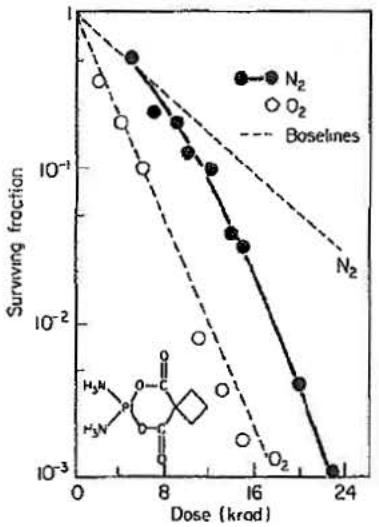


Figure 4. Radiopotentiation of *S. typhimurium* cells at 25°C by 200 μM carboplatin. Dashed lines are baseline sensitivities of hypoxic and oxic suspensions; irradiation is done under hypoxic (closed circles) or oxic conditions (open circles). Data redrawn from Richmond *et al.* (11) with permission of publisher.

prepared and serially diluted. Cells were plated in 60-mm diameter glass petri dishes in Basal Medium Eagle (BME) supplemented with L-glutamine, antibiotic-antimycotic and 15% fetal bovine serum. The cells, plated in numbers expected to produce approximately 100 colony-forming units (CFU) per dish following treatment, were permitted to attach during a 2.5 hour incubation at 37°C. The media was then carefully removed from the dishes and 5 ml of either Hank's balanced salt solution (HBSS) or HBSS containing carboplatin was added to the dishes. The petri dish covers were removed and the dishes were placed in aluminum chambers immersed in a 37°C water bath. The chambers were sealed, degassed by pumping, and back-filled with 95% nitrogen plus 5% CO_2. The pumping and back-filling was repeated three additional times at 15 minute intervals. After 1 hour the chambers were placed under a G.E. Maxitron-300 X-ray machine operating at 300 KVp and 20 mA (7.25 Gy/minute) and the cells were irradiated at 37°C. Immediately following irradiation, the dishes were removed from the chambers and HBSS was aspirated from the attached cells. The dishes were washed with 5 ml of HBSS, overlayed with 5 ml of fresh complete media, and returned to the CO_2 incubator for 7 days of growth. Survival was determined by standard CFU analysis. The toxicity resulting from the drug alone was ascertained using unirradiated drug-treated controls and log surviving fraction was plotted as a function of radiation dose. The combined modality survivals were adjusted for effects of the drug alone.

The results illustrated in Figure 5 indicate that an ER of approximately 1.8 results when a 500 μM concentration of carboplatin is administered to V79 cells for 1 hour at 37°C prior to and during irradiation. This resulting ER is produced with a drug concentration that has some toxicity since the survival fraction is 0.55 from carboplatin alone. Although this enhancement is larger than values reported for cisplatin at equal levels of toxicity, the drug dose required (500 μM) is approximately 50 times the levels of cisplatin which are practicable. These concentrations of carboplatin probably exceed those attainable in patients but the effects of $C \times t$ (concentration × time) in tumors would be expected to produce several orders of magnitude greater cytotoxicity from the drug alone.

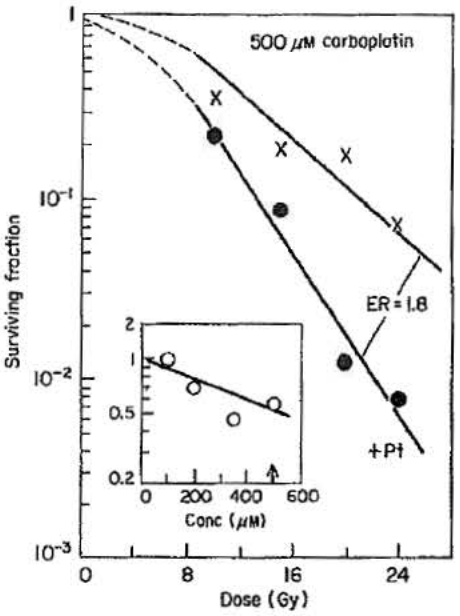


Figure 5. Radiosensitization of hypoxic V79 cells by 500 μM carboplatin (closed circles; D_0 = 3.80 Gy; ER = 1.8) compared to hypoxic baseline without drug (× 's; D_0 = 680 Gy). Combined modality line is corrected for toxicity from the drug alone (open circles). Cells were exposed to carboplatin for 1 hour at 37°C before irradiation.

In order to determine if carboplatin potentiates radiation therapy in a tumor system, experiments were performed utilizing a mouse mammary adenocarcinoma (MTG-B) transplanted in the flanks of 6-week-old female C3H/HeN (20 gram) mice. Tumor cell suspensions, prepared from tumors excised from passage mice using a Snell cytosieve and containing approximately 15% cells by volume in 0.05 ml BME, were injected subcutaneously. The inoculation site was palpated daily until tumors appeared and the diameters of the tumors were measured daily in two perpendicular dimensions using a template. Tumor volumes were calculated using the average of the two diameters to estimate the radius of a sphere.

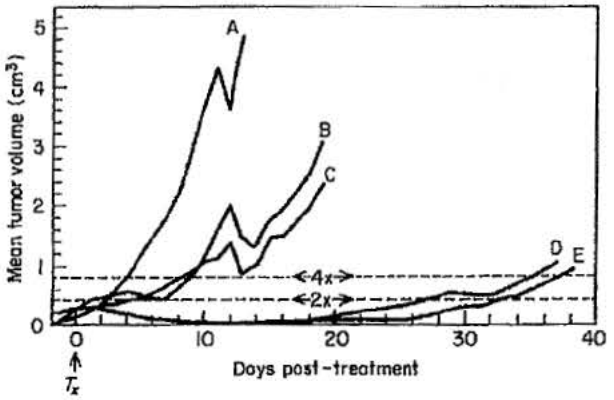


Figure 6. Mean tumor volumes for MTG-B growing in flanks of C3H mice as a function of days post treatment with carboplatin plus or minis radiation. Group A (untreated controls); B (drug alone, 60 mg/kg carboplatin i.p.); C (radiation alone, 20 Gy); D (carboplatin injected 30 minutes pre-irradiation); E (carboplatin injected immediately after irradiation).

An example of a combined modality experiment using tumor growth delay as an endpoint is illustrated in Figure 6. In this experiment tumor bearing mice were randomized into 5 groups and each treatment group contained 11 mice. Tumors were treated on the days when they reached average diameters between 7–8 mm (0.2 cm^3). Animals receiving drug alone (Group B, Figure 6) received i.p. injections of freshly prepared carboplatin (60 mg/kg body weight) in a concentration of 6 mg/ml of 0.9% NaCl. Animals receiving radiation alone (Group C) were anesthetized with sodium pentabarbitol (Nembutal; 60 mg/kg body weight) 5 minutes before a single dose of 20 Gy X-rays was delivered locally to the tumor. The tumors were subcutaneous and mobile. The tumors were pulled away from the body of the mouse and irradiated while centered under a 1.5 cm diameter cone which defined the X-ray field. The G.E. Maxitron-300 X-ray machine operated with 3 ml Al filtration, 140 KVp and 20 mA. The dose rate at the surface of the tumor was 5.17 Gy/min.

Tumors receiving the combined modality therapy were either injected with carboplatin 25 min before anesthetization and 30 min before irradiation (Group D) or injected immediately (within 1 minute) after irradiation (Group E). Tumor growth delay (TGD) was defined as the time in days for tumors to grow to 2× or 4× the initial treatment volumes. The resulting TGD values for the combined modality groups D (27 d, 35 d) and E (33 d, 37 d) are greater than predicted by the additive effects using the TGD for carboplatin alone (5 d, 9 d) plus the TGD for radiation alone (5 d, 8 d). Unlike similar studies with cisplatin (33) or the platinum analog JM-10 (E. B. Douple, unpublished data), there appears to be no significant difference between the platinum given before irradiation compared to platinum injected after irradiation. This may be an indication that the levels of carboplatin, at the times of irradiation selected, are below the limits of concentration required for hypoxic cell radiosensitization. Alternative explanations exist, however metabolic modification of the carboplatin might be required to permit interaction with the radiation and the 30 minutes before irradiation might not be sufficient time to permit these changes to occur.

These results are encouraging in that they demonstrate a therapeutic potentiation when a single dose of carboplatin is combined with a single dose of radiation. Further studies are required to investigate the use of more clinically relevant multiple dose (fractionation of drug and radiation) protocols, to examine carboplatin pharmacokinetics in the tumors and to evaluate the influence of timing between administration of the drug and irradiation. In addition, since experiments have shown a potentiation of low dose rate radiation (brachytherapy) by infused, low dose cisplatin (30), the potential for interaction under these conditions should be explored using carboplatin.

In our experiments no significant enhancement of skin damage was observed in the irradiated field. This absence of an effect in a clinically relevant normal tissue has been noted in other studies which combined cisplatin with radiation (27, 29, 34). A small enhancement of skin damage was reported in two studies (62, 63). The absence of significant enhancement of skin damage is especially encouraging since relatively high levels of platinum have been measured in mouse skin following injections of cisplatin (64). In other studies, duodenal crypt cells in mouse intestine have shown a moderate enhancement of radiation-induced damage when cisplatin was combined with irradiation under certain conditions (29, 30, 65, 68). Similar studies have not been reported for carboplatin and need to be initiated. Furthermore, careful monitoring of normal tissue responses in clinical trials will be required to identify any potential complications (69, 70).

Levels of total platinum have been measured in human malignant melanoma xenografts

in immune-suppressed mice (E. B. Douple and J. J. Roberts, unpublished data) following injections of 60 mg/kg carboplatin. At 30 mins post-injection of carboplatin platinum analysis by atomic absorption spectrometry recorded levels of 3.4 μg/g of wet tissue. Assuming that 1 g of tissue is equivalent to 1 ml of solvent, this corresponds to an approximate platinum concentration of 17.5 μM. In these same studies, levels of total platinum recorded following injection of 1/6× the dose of cisplatin (10 mg/kg) were approximately 1/6× levels attained with carboplatin. At this time the species responsible for the interaction with radiation is not known. The production of the appropriate platinum species may be different in tumors *in situ* compared to cultured cells.

A level of 6.4 μg platinum per gram of wet tissue was recorded for a human squamous cell carcinoma (71) and this exceeds the level of cisplatin required to produce radiosensitization or potentiation in cultured cells. It is interesting that in this cited study platinum concentrations in tumors were higher at 6 hours following injection of 100 mg/m^2 cisplatin than at 1 hour and 24 hours, and much higher than intravascular plasma platinum levels at the same time. Peak plasma levels of 31 μM total platinum and 15 μM ultrafilterable (free) platinum have been reported in patients after a dose of only 150 mg/m^2 of carboplatin (72). Since clinical doses in excess of 400 mg/m^2 of carboplatin are tolerated (53, 54) it is conceivable that platinum levels will be of the magnitude required for interaction with radiation, and free platinum will persist for longer time periods following carboplatin administration compared to cisplatin (55). Knowledge of the pharmacokinetics of the appropriate platinum species will be required in order to design the optimum combined modality treatment schedule. The biphasic decay of platinum concentrations in serum includes a terminal component with a half-life of several days (55). A plateau of tissue concentration after 24 hours may persist for several days. Whether the platinum in these long-lived compartments is not bound and still capable of interacting with radiation is not known at this time.

The administration of cisplatin is currently being coordinated with radiation therapy in a number of clinical studies intending to exploit the interaction of platinum with radiation. These include the treatment of brain tumors (43, 44), head and neck tumors (5, 43, 48), malignant melanomas (48) and bladder cancers (49). The results of these trials are preliminary and most of the studies are testing toxicity of the combined treatment rather than evaluating the efficacy of the new protocol compared to the effects of either agent alone. However, the results show promise in that this combination may be resulting in some improved responses of the patients' tumors to therapy, including the eradication of bulky disease or the reduction of bulky tumors to a level potentially manageable by surgery or higher doses of radiation (5). It is important to remember that these clinical studies have been designed without knowing the precise mechanisms for the interactions or the optimum timing and dose relationships between the two modalities. As carboplatin is introduced into certain clinical trials it is appropriate to consider that it too can be coordinated with radiation therapy with the intent to exploit interactions between the two agents.

There is a defined need for improved local tumor control (73). However, experimental and clinical studies have suggested that enhanced effects on normal tissues often result when drugs are administered in close temporal proximity to radiation. This subject has been reviewed in numerous publications, most recently by Fu (74). To avoid potential problems of increasing the number and severity of early and late side effects to normal tissues a conservative approach would be to (a) use drugs without serious toxic effects on those critical tissues which are included in the radiation treatment volume or (b) avoid concomitant administration (75). However, the potential for platinum complexes,

including carboplatin, to increase the therapeutic ratio by (a) radiosensitization of hypoxic tumor cells and/or by (b) potentiating radiation effects via post-irradiation inhibition of PLD recovery in tumor cells, suggests that platinum antitumor drugs, including carboplatin, may have an important role to play in an approach which combines the two agents in an appropriate fashion and close in time. Interactions between carboplatin and radiation might play an important role in meeting the challenging need for more effective local tumor control.

Acknowledgements

The authors thank Diane Daddario Hatch, Ellen Jones and Traci Byrne for their technical assistance and Johnson Matthey Research Centre and Johnson Matthey Pharmaceutical Research for partial support of this project.

References

1. Richmond, R. C. & Powers, E. L. (1976) Radiation sensitization of bacterial spores by *cis*-dichlorodiammineplatinum(II). *Radiat. Res.* **68:** 20–23.
2. Douple, E. B. & Richmond, R. C. (1979) A review of platinum-complex biochemistry suggests a rationale for combined platinum-radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1335–1339.
3. Douple, E. B. & Richmond, R. C. (1980) Interactions between platinum coordination complexes and ionizing radiation. In: Prestayko, A. W., Crooke, S. T. & Carter, S. K. eds. *Cisplatin: Current Status and New Developments.* New York: Academic Press. pp. 125–147.
4. Douple, E. B. (1984) *Cis*-diamminedichloroplatinum(II): Effects of a representative metal coordination complex on mammalian cells. *Pharmac. Ther.* **25:** 297–326.
5. Coughlin, C. T. & Richmond, R. C. (1985) Platinum based combined modality approach for locally advanced head and neck carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.* **11:** 915–919.
6. Douple, E. B. (1985) The use of platinum chemotherapy to potentiate radiotherapy: preclinical results encourage clinical trials. *Platinum Metals Review* **29:** 118–125.
7. Ozols, R. F., Corden, B. J., Collins, J. & Young, R. C. (1984) Renal effects and clinical pharmacokinetics of high-dose (HD) cisplatin (P) (40 mg/m^2 QD × 5) in hypertonic saline. In: Hacker, M. P., Douple, E. B. & Krakoff, I. H. eds. *Platinum Coordination Complexes in Cancer Chemotherapy.* Boston: Martinus-Nijhoff. pp. 321–329.
8. Calvert, A. H., Harland, S. J., Newell, D. R., Siddik, Z. H., Jones, A. C., McElwain, T. J. Raju, S., Wiltshaw, E., Smith, I. E., Baker, J. W., Peckham, M. J. & Harrap, K. R. (1982) Early clinical studies with cis-diammine-1,1-cyclobutane dicarboxylate platinum II. *Cancer Chemother. Pharmacol.* **9:** 140–147.
9. Creaven, P. J., Madajewicz, S., Pendyala, L., Mittelman, A., Pontes, E., Spaulding, M., Arbuck, S. & Solomon, J. (1983) Phase I clinical trial of cis-dichloro-trans-dihydroxy-bis-isopropylamine platinum(IV) (CHIP). *Cancer Treat. Rep.* **67:** 795–800.
10. Richmond, R. C. (1984) Toxic variability and radiation sensitization by dichlordiammineplatinum(II) complexes in *Salmonella typhimurium* cells. *Radiat. Res.* **99:** 596–608.
11. Richmond, R. C., Khokhar, A. R., Teicher, B. A. & Douple, E. B. (1984) Toxic variability and radiation sensitization by Pt (II) analogs in *Salmonella typhimurium* cells. *Radiat. Res.* **99:** 609–626.
12. Douple, E. B. & Richmond, R. C. (1978) Platinum complexes as radiosensitizers of hypoxic mammalian cells. *Br. J. Cancer* **37,** Suppl. III: 98–102.
13. Barot, H. A., Laverick, M. & Nias, A. H. W. (1985) The radiomimetic properties of a platinum drug. *Br. J. Radiol.* **58:** 51–62.
14. Richmond, R. C., Curphey, T. J. & Katzenellenbogen, J. A. (1984) One approach to targeted platinum drug activity-design of a synthetic antiestrogen-Pt(II) complex. (Abstract) In: Hacker, M. P., Douple, E. B. & Krakoff, I. H. eds. *Platinum Coordination Complexes in Cancer Chemotherapy.* Boston: Martinus-Nijhoff, 262.
15. Bales, J. R., Sadler, P. J., Coulson, C. J., Laverick, M. & Nias, A. H. W. (1982) Hypoxic cell sensitization to

radiation damage by a new radiosensitizer: *Cis*-dichloro-bis(1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole-N3) Platinum (II) (FLAP). *Br. J. Cancer* **46:** 701–705.

16. Douple, E. B. & Teicher, B. A. (1984) Potentiation of cell kill by combining nitroimidazole-platinum complexes with radiation (Abstract). In: Hacker, M. P., Douple, E. B. & Krakoff, I. H. eds. *Platinum Coordination Complexes in Cancer Chemotherapy.* Boston: Martinus-Nijhoff. p. 355.
17. Adams, G. E. & Dewey, D. L. (1963) Hydrated electrons and radiobiological sensitization. *Biochem. Biophys. Res. Comm.* **12:** 473–477.
18. Zimbrick, J. D., Aruni Sukrochana, M. S. & Richmond, R. C. (1979) Studies on radiosensitization of *Escherichia coli* cells by *cis*-platinum complexes. *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1351–1354.
19. Stratford, I. J., Williamson, C. & Adams, G. E. (1980) Combination studies with misonidazole and a *cis*-platinum complex: cytotoxicity and radiosensitization *in vitro*. *Br. J. Cancer* **41:** 517–522.
20. Carde, P. & Laval, F. (1981) Effects of *cis*-dichlorodiammine platinum II and X-rays on mammalian cell survival. *Int. J. Radiat. Oncol. Biol. Phys.* **7:** 929–933.
21. Dritschilo, A., Piro, A. J. & Kellman, A. D. (1979) The effect of *cis*-platinum on the repair of radiation damage in plateau phase Chinese hamster (V79) cells. *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1345–1349.
22. Lindquist, K., Douple, E. B. & Richmond, R. C. (1982) Platinum drug modulation of radiation damage (Abstract). *Radiat. Res.* **91:** 408.
23. Brown, J. M., Biaglow, J. E., Hall, E. J., Kinsella, T. J., Phillips, T. L., Urtasun, R. C., Utley, J. F. & Yuhas, J. M. (1984) Sensitizers and protectors to radiation and chemotherapeutic drugs. *Cancer Treat. Symp.* **1:** 85–101.
24. Brown, J. M. (1984) Clinical trials of radiosensitizers: what should we expect? *Int. J. Radiat. Oncol. Biol. Phys.* **10:** 425–429.
25. Richmond, R. C., Zimbrick, J. D. & Hykes, D. L. (1977) Radiation-induced DNA damage and lethality in *E. coli* as modified by the antitumor agent *cis*-dichlorodiammineplatinum(II). *Radiat. Res.* **71:** 447–460.
26. Szumiel, I. & Nias, A. H. W. (1976) The effect of combined treatment with a platinum complex and ionizing radiation on Chinese hamster ovary cells *in vitro*. *Br. J. Cancer* **33:** 450–458.
27. Overgaard, J. & Kahn, A. R. (1982) Selective enhancement of radiation response in a C3H mammary carcinoma by cisplatin. *Cancer Treat. Rep.* **65:** 501–503.
28. Twentyman, P. R. Kallman, R. F. Brown, J. M. (1979) The effect of time between x-irradiation and chemotherapy on the growth of three solid mouse tumors. III. *cis*-diammine-dichloroplatinum. *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1365–1367.
29. Bartelink, H. & Kallman, R. F. (1983) The effects of cisplatin and irradiation on tumor, skin and gut in mice. In: Broerse, J. J., Barendsen, G. W., Kal, H. B. & van der Kogel, A. J. eds. *Tumour Biology and Therapy: Proceedings of the Seventh International Congress of Radiation Research.* Amsterdam: Martinus Nijhoff. pp. D7–03.
30. Fu, K. K., Rayner, P. A. & Lam, K. (1983) Modification of the effects of continuous low dose rate irradiation by chemotherapy. In: Broerse, J. J., Barendsen, G. W., Kal, H. B. & van der Kogel, A. J. eds. *Tumour Biology and Therapy: Proceedings of the Seventh International Congress of Radiation Research.* Amsterdam: Martinus Nijhoff. pp. D7–05.
31. Dionet, C. & Verrelle, P. (1984) Curability of mouse L1210 leukemia by combination of 5-fluorouracil, *cis*-diamminedichloroplatinum(II) and low doses of X-rays. *Cancer Res.* **44:** 652–656.
32. Douple, E. B. & Richmond, R. C. (1979) Radiosensitization of hypoxic tumor cells by *cis*- and *trans*-dichlorodiammineplatinum(II). *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1369–1372.
33. Douple, E. B. & Richmond, R. C. (1982) Enhancement of the potentiation of radiotherapy by platinum drugs in a mouse tumor. *Int. J. Radiat. Oncol. Biol. Phys.* **8:** 501–503.
34. Douple, E. B., Richmond, R. C. & Logan, M. E. (1977) Evaluation of the radiation-sensitizing potential of platinum coordination complexes in mammalian cells and in solid tumors. *Wadley Med. Bull. J. Clin. Hematol. Oncol.* **7:** 585–603.
35. Weichselbaum, R. R., Schmit, A. & Little, J. B. (1982) Cellular repair factors influencing radiocurability of human malignant tumors. *Br. J. Cancer* **45:** 10–16.
36. Weichselbaum, R. R., Nove, J. & Little, J. B. (1980) Radiation response of human tumor cells *in vitro*. In: Meyn, R. E. & Withers, H. R. eds. *Radiation Biology in Cancer Research.* New York: Raven Press. pp. 345–351.
37. Weichselbaum, R., Malcolm, A. W. & Little, J. B. (1982) Fraction size and the repair of potentially lethal radiation damage in a human melanoma cell line. *Radiology* **142:** 225–227.
38. Weichselbaum, R. R. & Little, J. B. (1982) The differential response of human tumours to fractionated radiation may be due to a post-radiation repair process. *Br. J. Cancer* **46:** 532–537.
39. Weichselbaum, R. R., Little, J. B. & Nove, J. (1977) Response of human osteosarcoma *in vitro* to irradiation: Evidence for unusual cellular repair activity. *Int. J. Radiat. Biol.* **31:** 295–301.

40. Little, J. B. (1969) Repair of sublethal and potentially lethal radiation damage in plateau phase cultures in human cells. *Nature* **224:** 804-806.
41. Hahn, G. M. & Little, J. B. (1972) Plateau-phase cultures of mammalian cells: an *in vitro* model for human cancer. *Curr. Topics Radiat. Res. Q,* **8:** 39-83.
42. Murthy, A. K., Rossof, A. H., Anderson K. M. & Hendrickson, F. R. (1979) Cytotoxicity and influence on radiation dose response curve of *cis*-diamminedichloroplatinum(II) (*cis*-DDP). *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1411–1415.
43. Stewart, D. J., Leavens, M., Maor, M., Feun, L., Luna, M., Bonura, J., Caprioli, R., Loo, T. L. & Benjamin, R. S. (1982) Human central nervous system distribution of *cis*-diamminedichloroplatinum and use as a radiosensitizer in malignant brain tumors. *Cancer Res.* **42:** 2474–2479.
44. Stewart, D. J., Wallace S., Feun, L., Leavens, M., Young, S. E., Handel, S., Mauligit, G. & Benjamin, R. S. (1982) A phase I study of intracarotid artery infusion of *cis*-diamminedichloroplatinum(II) in patients with recurrent malignant intracerebral tumors. *Cancer Res.* **42:** 2059-2062.
45. Creagen, E. T., Fountain, K. S., Frytal, S., DeSanto, L. W. & Earle, J. D. (1981) Concomitant radiation therapy and *cis*-diamminedichloroplatinum(II) in patients with advanced head and neck cancer. *Med. Pediatr. Oncol.* **9:** 119–120.
46. Pinedo, H. M., Karin, A. B. M. F., van Vliet, W. H., Snow, G. B. & Vermorken, J. B. (1983) Daily *cis*-dichlorodiammineplatinum(II) as a radio-enhancer: a preliminary toxicity report. *J. Cancer Res. Clin. Oncol.* **105:** 79–82.
47. Coughlin, C. T., Grace, M., O'Donnell, J. F., LeMarbre, P. J., Morain, W. D., Geurkink, N. A. & McIntyre, O. R. (1984) Combined modality approach in the management of locally advanced head and neck cancer. *Cancer Treat. Rep.* **68:** 591–597.
48. Leipzig, B. (1983) Cisplatin sensitization to radiotherapy of squamous cell carcinomas of the head and neck. *Am. J. Surg.* **146:** 462–465.
49. Reimer, R. R., Gahbauer, R., Bukowski, R. M., Hewlett, J. S., Groppe, C. W., Weick, J. K. & Antunez, A. R. (1981) Simultaneous treatment with cisplatin and radiation therapy for advanced solid tumors: a pilot study. *Cancer Treat. Rep.* **65:** 219–222.
50. Herr, H. W., Yagoda, A., Batata, M., Sogani, P. C. & Whitmore, W. F. (1983) Planned preoperative cisplatin and radiation therapy for locally advanced bladder cancer. *Cancer* **52:** 2205-2208.
51. Zak, M. & Drobnik, J. (1971) Effect of *cis*-dichlorodiammineplatinum(II) on the postirradiation lethality in mice after irradiation with X-rays. *Strahlentherapie* **142:** 112–115.
52. Wodinsky, I., Swiniarski, J., Kensler, C. J. & Venditti, J. M. (1974) Combination radiotherapy and chemotherapy for P388 lymphocytic leukemia *in vivo*. *Cancer Treat Rep.* **4:** 73–97.
53. Calvert, A. H., Harland, S. J., Harrap, K. R., Wiltshaw, E. & Smith, I. E. (1984) JM8 development and clinical projects. In: Hacker, M. P., Douple, E. B. & Krakoff, I. H. eds. *Platinum Coordination Complexes in Cancer Chemotherapy*. Boston- Martinus Nijhoff. pp. 240–252.
54. Van Echo, D. A., Egorin, M. J., Whitacre, M. Y., Olman, E. A. & Aisner, J. (1984) Phase I clinical and pharmacologic trial of carboplatin daily for 5 days. *Cancer Treat. Rep.* **68:** 1103-1114.
55. Curt, G. A., Grygiel, J. J. Corden, B. J., Ozols, R. F. Weiss, R. B., Tell, D. T., Myers, C. E. & Collins, J. M. (1983) A phase I and pharmacokinetic study of diamminecyclobutane-dicarboxylatoplatinum (NSC241240). *Cancer Res.* **43:** 4470–4473.
56. Siddik, Z. H., Newell, D. R., Boxall, F. E., Jones, M., McGhee, K. G. & Harrap, K. R. (1984) Biliary excretion, renal handling and red cell uptake of cisplatin and CBDCA in animals. In: Hacker, M. P., Douple, E. B. & Krakoff, I. H. eds. *Platinum Coordination Complexes in Cancer Chemotherapy*. Boston: Martinus Nijhoff. pp. 90–102.
57. Richmond, R. C., Douple, E. B., Bergquist, B. L., Chang, J. C. & Khokhar, A. R. (1984) Effective radiation sensitization of hypoxic. *S. typhimurium* cells by slightly toxic Pt(II)-complexes. (Abstract) In: Hacker, M. P., Douple, E. B. & Krakoff, I. H. eds. *Platinum Coordination Complexes in Cancer Chemotherapy*. Boston: Martinus Nijhoff. p. 351.
58. Boven, E., van der Vijgh, W. J. F., Nauta, M. M., Schluper, H. M. M. & Pinedo, H. M. (1985) Comparative activity and distribution studies of fine platinum analogues in nude mice bearing human ovarian carcinoma xenografts. *Cancer Res.* **45:** 86–90.
59. Richmond, R. C. & Simic, M. G. (1978) Effect of radiation on *cis*-dichlorodiammineplatinum(II) and DNA in aqueous solution. *Br. J. Cancer* **37,** Suppl. III: 20–23.
60. Butler, J., Hoey, B. M. & Swallow, A. J. (1985) The radiation chemistry of some platinum-containing radiosensitizers and related compounds. *Radiat. Res.* **102:** 1–13.
61. Chibber, R. (1984) Radiosensitizing and cytotoxic action of some Rh(II) carboxylates *in vitro*: a comparison

with Pt (II) complexes. Ph.D. Dissertation, Department of Chemistry, Hatfield Polytechnic, Hatfield, Hertfordshire, England.

62. Douple, E. B., Eaton, W. L. Jr. & Tulloh, M. E. (1979) Skin radiosensitization studies using combined *cis*-dichlorodiammineplatinum(II) and radiation. *Int. J. Radiat. Oncol. Biol. Pnys.* **5:** 1383–1385.
63. von der Maase, H. (1984) Effect of cancer chemotherapeutic drugs on the radiation-induced skin reactions in mouse feet. *Br. J. Radiol.* **57:** 697–707.
64. Benard, P., DesPlanches, G., Macquet, J. P. & Simon, J. (1983) Whole-body autoradiographic study of the distribution of ^{195m}Pt in healthy and tumor-bearing mice treated with labelled cisplatin. *Cancer Treat. Rep.* **67:** 457–466.
65. Schenken, L. L., Burholt, D. R., Hagemann, R. F. & Kovacs, C. J. (1979) Combined modality oncotherapies: Cell kinetic approaches for avoidance of gastrointestinal toxicity. In: Vaeth, J. M. ed. *Frontiers of Radiation Therapy and Oncology.* Basel: Karger. pp. 82–101.
66. Luk, K. H., Ross, G. Y., Phillips, T. L., Goldstein, L. S. (1979) The interaction of radiation and *cis*-diamminedichloroplatinum(II) in intestinal crypt cells. *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1417–1420.
67. Burholt, D. R., Schenken, L. L., Kovacs, C. J. & Hagemann, R. F. (1979) Response of the murine gastrointestinal epithelium to *cis*-dichloro-diammine-platinum II: radiation combinations. *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1377–1381.
68. Phillips, T. L. (1980) Clinical and experimental alternations in the radiation therapeutic ratio caused by cytotoxic chemotherapy. In: Meyn, R. E. & Withers, H. R. eds. *Radiation Biology in Cancer Research.* New York: Raven Press. pp. 567–588.
69. Golding, R. P. & Van Zanten, T. E. G. (1983) Lung destruction after *cis*-platinum radiosensitization. *Br. J. Radiol.* **56:** 281–282.
70. Nias, A. H. W. (1983) Toxicity of platinum drug radiosensitization. *Br. J. Radiol.* **56:** 605.
71. Mattox, D. E., Sternson, L. A., von Hoff, D. D., Kuhn, J. G. & Repta, A. J. (1983) Tumor concentration of platinum in patients with head and neck cancer. *Otolaryngol. Head Neck Surg.* **91:** 271–275.
72. Wooley, P. V., Priego, V. M., Luc, P. V. T., Rahman, A. & Schein, P. S. (1984) Clinical pharmacokinetics of diammine[1,1-cyclobutane-dicarboxylato-(2)]-0,0′ platinum (CBDCA). In: Hacker, M. P., Douple, E. B. & Krakoff, I. H. eds. *Platinum Coordination Complexes in Cancer Chemotherapy.* Boston: Martinus Nijhoff. pp. 82–89.
73. Suit, H. (1982) Potential for improving survial rates for the cancer patient by increasing the efficacy of treatment of the primary lesion. *Cancer* **50:** 1227–1234.
74. Fu, K. K. (1985) Biological basis for the interaction of chemotherapeutic agents and radiation therapy. *Cancer* **55:** 2123–2130.
75. Tubiana, M., Arriagada, R. & Cosset, J. M. (1985) Sequencing of drugs and radiation: The integrated alternating regimen. *Cancer* **55:** 2131–2139.
76. Eagan, R. T., Lee, R. E., Frytak, S., Fleming, T. R., Gregan, E. T., Ingle, J. N. & Kvols, L. K. (1979) Randomized trial of thoracic irradiation plus combination chemotherapy for unresectable adenocarcinoma and large cell carcinoma of the lung. *Int. J. Radiat. Oncol. Biol. Phys.* **5:** 1401–1405.