2. **Head and Neck Cancer**

Introduction

Data from the Swedish Cancer Registry show, that 960 cancers of the head and neck region (lip, oral cavity, pharynx, larynx, paranasal sinus, nasal cavity) were diagnosed in 2000 in Sweden. That corresponds to about 2 per cent of all newly diagnosed cancers. The number of cases in 1992 was 912. In 2000, these diagnoses were registered as the primary cause of death in 314 cases and in 1992 in 301 cases. Patients presenting with a squamous cell carcinoma of the head and neck generally have significant co-morbidity factors due to age and a number of other risk factors such as smoking and drinking habits. Cancers of the head and neck are mainly a locoregional disease at diagnosis and the incidence of distant metastases is low. Surgery, external beam radiotherapy and brachytherapy or combinations thereof constitute the basis for radical treatment. Due to the close relation to a variety of vital structures the treatment of these cancers becomes a challenge for both radiotherapists and surgeons. For unresectable tumours, radiotherapy offers a potential for cure. For resectable tumours radiotherapy may offer organ preservation and a better cosmetic outcome as well as a means to treat subclinical disease, with less morbidity than extended surgery.

Despite major efforts to treat these patients, a substantial proportion of the tumours can not be controlled. Considerable efforts have been expended to find more effective therapies. Increased aggressiveness of therapy might be one way towards better outcomes of therapy. However, this is frequently not possible, since already conventional therapy gives considerable side-effects. It is not obvious that patients, whose medical condition often is compromised by other diseases, will be able to tolerate a significantly increased toxicity.

Summary of the earlier report, SBU 129/2

The synthesis of the literature on radiotherapy for head and neck cancer was based on 424 scientific articles, including 3 meta-analysis, 38 randomized studies, 45 prospective studies, and 246 retrospective studies.

Conclusions

- The literature review shows that radiotherapy, either alone or in combination with surgery, plays an essential role in treating head and neck cancers. When tumours are localized, many tumour patients can be cured by radiotherapy alone and thereby maintain full organ function.
- Current technical advancements in radiotherapy offer the potential for better local tumour control with lower morbidity. This, however, will require more sophisticated dose planning resources.
- To further improve treatment results for advanced tumours, other fractionation schedules, mainly hyperfractionation, should be introduced. This increases the demands on staff resources for radiotherapy.
- The combination of radiotherapy and chemotherapy should be subjected to further controlled studies involving a sufficiently large number of patients.
- Interstitial treatment (in the hands of experienced radiotherapists) yields good results for selected cancers. The method should be more generally accessible in Sweden.
- Intraoperative radiotherapy should be the targeted for further studies and development.

Discussion

One aim of the previous report was to establish the role of radiotherapy for treatment of squamous cell carcinomas at different sites in the head and neck region. The reason for this is the different properties that tumours of different sites exhibit regarding clinical behaviour, prognosis, resectability etc. For a majority of the conclusions regarding site specific treatments the evidence is based on retrospective studies, due to the lack of randomized controlled clinical trials. Randomized, site specific, trials

in head and neck cancer are rare, possibly with the exception of nasopharyngeal and laryngeal tumours.

The majority of randomized trials concern squamous cell carcinomas in the head and neck region in general. Commonly the different sites are reported individually as subgroups but the number of tumours within each site is often too small to give adequate statistical power for reaching meaningful conclusions.

Regarding treatment delivery the testing of different fractionation schedules and combinations of radiotherapy and chemotherapy have been the objects of randomized trials. In contrast, interstitial brachytherapy has proven to be an effective therapy in some situations, but no trial has been performed comparing brachytherapy to external beam therapy.

Radiotherapy of different tumour sites in the head and neck

Mobile tongue

It was concluded that radiation alone is an effective therapy in cases with small to moderately advanced tumours. The radiotherapy should preferably be delivered as a combination of external and interstitial therapy or perhaps interstitial only. The potential for curing advanced tumours is limited.

Base of tongue

In most cases early tumours can be successfully treated with radiation alone. The role of interstitial radiotherapy has not been established. The prognosis of advanced tumours is comparatively unfavourable. Hyperfractionated radiotherapy seems to improve tumour control.

Tonsil

Similar conclusions as for base of tongue but interstitial brachytherapy may have a more important role.

Nasopharynx

Radiotherapy alone is highly effective in early tumours provided a high quality treatment planning and delivery. Local boost treatment may decrease the risk for local failure. Combinations with chemotherapy have not been proven to improve results.

Hypopharynx

The results of radiotherapy for early tumours are relatively good but the results of conventional fractionation for advanced tumours are poor. Hyperfractionation studies have shown better results.

Larynx

Radiotherapy is the dominating therapy for early tumours of vocal cords and is also an alternative to surgery in carcinoma in situ. The treatment results are good. In advanced tumours the treatment results are worse but a large proportion of those survivors may retain the voice. Hyperfractionated radiotherapy leads to improved treatment results. Similar conclusions were drawn for supraglottic carcinomas. However, the treatment results are overall less favourable.

Future development of radiotherapy

Altered fractionation

Modern techniques for localization and staging of tumours resulting in less uncertainty in target definition have a large potential for improving treatment results with better tumour control and/or less side effects. This is also the case with improved treatment planning and delivery.

Prolongation of overall treatment time negatively influences the tumour control probability. Multiple small fractions per day with smaller doses per fraction, higher total dose and same overall treatment time may give better results and should be used more frequently. Intraoperative treatment may play a role in the future.

Combination of chemotherapy and radiotherapy

Neo-adjuvant chemotherapy has not proven beneficial in the treatment of head and neck cancers. Concomitant chemotherapy seems to improve the tumour effect but seems also to increase the side effects.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
M	1/426	2/3 499	–	**3/3 925**
C	6/2 492	24/4 593	8/658	**38/7 743**
P	8/1 194	25/983	12/365	**45/2 542**
R	47/32 769	150/28 902	49/3 293	**246/64 964**
L	19	19	–	**38**
O	20	30	4	**54**
Total	**101/36 881**	**250/37 977**	**73/4 316**	**424/79 174**

Assessment of new literature

Search method and selections

For revising the conclusions of the previous study it was concluded that randomized clinical studies or meta-analysis with individual patient data would be required. For that reason, only studies fulfilling these criteria were selected for this report.

Search for literature was made in Medline for the period 1994–August 2001. The key words (MeSH) were: "head and neck neoplasms", "mouth neoplasms", "laryngeal neoplasms" and "pharyngeal neoplasms" in combination with "radiotherapy" in text or as subheading. The search was confined to randomized, controlled studies and meta-analysis written in the English language. Additional search was made in the Cochrane Library.

A total number of 239 references were retrieved with this method. Abstracts were reviewed from all papers. Of these, 117 were not reviewed further for the reason of not being relevant for the questions to be answered in this report or not being randomized controlled studies or meta-analysis, etc. The remaining 122 scientific articles were reviewed. For studies addressing the effectiveness of radiotherapy, only studies comprising a minimum of 100 patients were considered useful for this report. Studies with fewer patients than that were not further reviewed.

For answering questions regarding prophylactic measures to decrease side effects, a lower number of patients (50) was accepted since the main end point usually was subjective symptom relief. In such case the effects can be large and more readily detected even with a comparatively small number of patients.

The reasons for exclusion of 196 articles from further analysis in the present review were grouped as follows:

Group		
A	50	not randomized studies
B	67	topics or end-points not relevant to the aim of this study
C	4	preliminary reports where the final report is included in this study
D	3	lack of quality
E	1	duplicate article published in a different journal
F	71	patient numbers too small for making meaningful interpretation possible

Overview of new studies

Severe acute side effects of radiotherapy can be dose limiting in some situations e.g. in patients with a poor performance status or in cases where the acute side effects are so severe that they will leave irreversible changes in tissues. However, in general severe late side effects of radiotherapy are considered to be dose limiting. There is no consensus on, what frequency of each type of severe late side effect, that would be "acceptable" in a group of patients but severe consequences from such side effects make the tolerated frequency low. The maximum tolerated radiation dose with conventional fractionation is not well established. 66–70 Gy is commonly considered a standard treatment in clinical trials. The long-term experience from such treatment is extensive and it can probably be considered to produce an effect- vs. side-effect-ratio that is acceptable in the eyes of most radiation oncologists. However, the frequency of severe complications may vary considerably between centres due to treatment techniques, the volumes of normal tissue included, tumour stage etc.

In the present report it is considered that new recommendations (compared with SBU 129/2) on treatment strategies can be given if one or both of the following has been shown:

- Better tumour control with the same or a lower frequency of severe side effects (WHO grade 3–4).
- Same tumour control but fewer severe side effects.
- Improved organ preservation with no increase in late side effects.
- Improved overall survival.

Combined treatments (another treatment modality added to radiotherapy), showing better tumour control and more side effects can usually not distinguish the additional tumour effect from the effect of increasing the radiation dose. Such studies generally need further and more extensive studies to prove a demonstrate fit for the patient and the "number needed to treat" for a certain intervention must be carefully considered. The "number needed to treat" to ascertain a certain benefit must also be put in relation to the nature and frequency of the extra toxicity that is inflicted on the patients.

Combination of chemotherapy and radiotherapy

Overview 1 (after the list of references)

The rationale for adding chemotherapy to radiotherapy of head and neck cancers is to sensitize tumours more than the normal tissues to radiation and/or eradicating subclinical distant metastases. Three major routes have been followed: neoadjuvant, concomitant and adjuvant chemotherapy, sometimes in combination.

Common features of the individual trials concerning chemotherapy and radiation are small numbers of patients and/or a short follow-up. In many cases no quality assurance procedure is reported and, late side effects are poorly, or not, described or analysed, sometimes as a consequence of the short follow-up. In fact, the radiotherapy procedure is very often poorly described and dose prescription, radiotherapy technique and treatment volumes are frequently not reported. The reason for early closure of some studies has been the observation of a statistically significant difference

between study groups at an interim analysis. The scheduling and criteria for these interim analysis are sometimes not reported. The combination of such factors makes the interpretation of the results difficult and it has a major impact on the strength of evidence. It has to be noted that many of the trials in this report were designed and started before the concept of "good clinical practice" (GCP) was widely adopted and trials that show a higher degree of conformity to these quality criteria are to be expected in the future.

All sites except nasopharynx

meta-analysis

The overall effect of chemotherapy has been studied in a meta-analysis where squamous cell carcinomas of the head and neck where treated with radiotherapy with or without chemotherapy [33]. Trials on nasopharyngeal carcinomas alone were excluded. The effect on survival was statistically significant (4 per cent at two and five years). In neo-adjuvant or adjuvant settings the overall effect of adding chemotherapy is not statistically significant while the estimated increase in survival with concomitant chemotherapy is 8 per cent. However, 14 heterogeneous studies (out of 63) account for a comparatively large part of the total effect but only 11 per cent of the patients. The remaining effect decreases when these studies are excluded from the analysis. Multi-agent chemotherapy was more effective than single agent. Further subgroup analysis showed a benefit for neo-adjuvant chemotherapy if only those trials using cisplatinum and 5-fluorouracil were considered.

Another meta-analysis in the same publication [33] evaluated the effect of concomitant versus neo-adjuvant chemotherapy. No significant difference was detected.

The third meta-analysis in the same paper was aimed at investigating the results of combined chemotherapy and radiotherapy versus primary surgery and post-operative radiotherapy in locally advanced carcinomas of the larynx and hypopharynx. The five year survival was reduced by 6 per cent in the chemo-radiotherapy group (not statistically significant) while more than 50 per cent of the surviving patients in this group lived with a preserved larynx.

In none of the three meta-analysis, any evaluation of side effects was performed.

Individual trials of radiotherapy and concomitant chemotherapy

This overview of the literature includes several studies [13,18,21,23,24, 29,32,37,41] that were updated and re-analysed in the meta-analysis [33]. The more recent literature includes six trials with chemotherapy in a concomitant setting [1,4,6,12,20,35]. A statistically significantly increased local tumour control and/or overall survival is shown in all but one, where altered fractionation with acceleration was used in both treatment arms [35]. In one study an unconventional fractionation with a prolonged overall treatment time was used [41]. In the same study the survival in the control group was unusually low. In those studies where the incidence of distant metastases was reported only one showed a statistically significantly lower incidence for chemotherapy-treated patients and in that study the number at risk was very small [20]. In most cases cisplatin/carboplatin and 5-fluorouracil was used [1,4,6,20,21,29,35,41]. The acute radiation side effects were reported to be worse for combined radiochemotherapy in six out of eight trials. In the remaining trial they were reported to be similar. The acute radiation side effects must be added to the systemic chemotherapy side effects. Commonly, WHO grade 3–4 haematological toxicity was encountered as well as some septic deaths. Severe late radiation side effects were reported to be more frequent in five trials, similar in one and not reported in two. In some trials it was not obvious how and at what interval the follow-up regarding late side effects was performed. The short follow-up of most studies could lead to serious underestimation. Severe fibrosis of the neck is one late side effect that is infrequently seen after radiotherapy alone but seems to be more frequent after the combination therapy [6].

Mitomycin C was used in two small studies [12,18] showing improved locoregional control and in one study improved survival. The acute radiation side effects were worse with the combination than with radiation alone. No firm conclusions can be drawn from the reports of late side effects. The haematological side effects were considerable. The rationale for using mitomycin C was, that it is considered to mainly sensitize hypoxic cells to radiotherapy.

Trials of radiotherapy and neo-adjuvant chemotherapy

Five trials concerning radiotherapy with/without neo-adjuvant chemotherapy were included in this report [13,23,24,32,37]. All of them were included in the meta-analysis [33]. All except one [13], that included both patients that received radiotherapy only as primary treatment and radiotherapy post-operatively, were negative in regard to the additional effect from chemotherapy. Late side effects were not reported. One larynx preservation study showed no significant difference in survival whether primary surgery with post-operative radiotherapy or neo-adjuvant chemotherapy and radiotherapy only was used for treatment [23]. In the latter group 28 per cent of the patients were alive with preserved larynx at three years.

The literature shows that:

- Concomitant administration of radiotherapy and chemotherapy improves the overall survival in non-nasopharyngeal head and neck cancers. The magnitude of the effect on overall survival is estimated to be 8 per cent in the meta-analysis, but it is hard to reliably estimate because of heterogeneous results.
- In addition to the specific chemotherapy side effects, the acute radiation side effects are more severe with combined therapy.
- The severe late radiation side effects are less well studied and often not evaluable but seem to be more frequent with combination therapy.
- There is no evidence that concomitant chemotherapy acts as a specific sensitizer of tumour cells, i.e. not sensitizing normal tissues.
- Neo-adjuvant and adjuvant chemotherapy has not demonstrated an increase in overall survival in non-nasopharyngeal head and neck carcinomas.
- Larynx preservation is possible in 50 per cent of patients with hypopharyngeal cancers when treated with neo-adjuvant chemotherapy and radical radiotherapy compared with surgery and post-operative radiotherapy. The overall survival may be lower in the conservatively treated patients.

Nasopharynx

Carcinoma of the nasopharynx is an endemic disease in parts of the world. In such regions nasopharyngeal cancer is one of the most frequent malignancies in the population and the high-grade tumours (WHO 2–3) are overwhelmingly predominant. The proportion of more differentiated carcinomas is larger in low incidence regions. Sweden is a country with low incidence. Possibly the two forms represent different diseases. Five studies on combination of radio- and chemotherapy are included in this report [2,3,8,9,26]. One study [8] is a later follow-up of a subgroup [9].

One study concerns radiotherapy with or without concomitant and adjuvant chemotherapy [2]. This study was closed early due to an early, planned, interim analysis showing a major survival benefit for those receiving chemotherapy. The study is small with a high proportion of patients randomized, who were ineligible. The follow-up is short (33 per cent <2 years) and late side effects are thus not evaluated. Compliance to the chemotherapy protocol was low. The severe acute side effects were more frequent in the chemotherapy treated patients. Split pause in the radiotherapy was allowed, if judged necessary due to side effects. The frequency, distribution or lengths of such treatment interruptions are not reported. The "progression free survival" seems unusually low in the conventionally treated group. These factors make the results difficult to interpret.

In the remaining studies the effect of neo-adjuvant chemotherapy was evaluated. Combinations of cisplatin and 5-fluorouracil [26], epirubicin, cisplatin and bleomycin [3], or epirubicin and cisplatin were investigated [8,9]. In no statistically significant difference in survival was identified but patients treated with neo-adjuvant chemotherapy had a significantly higher rate of disease/relapse free survival [3,26]. In a non-standard fractionation of the radiotherapy was used [8,9]. No statistically significant difference in overall or relapse free survival between the treatment groups could be detected. In studies reporting the frequency of distant metastases, no significant difference between groups was found. The chemotherapy seemed to only marginally affect the acute radiation effect. The reporting of late radiation side effects was the mostly absent. In one study the frequency of treatment related deaths was 8 per cent in the chemoradiotherapy group and 1 per cent in the radiotherapy alone group [3].

The literature shows that:

- A combination of concomitant and adjuvant chemotherapy in naso-pharyngeal cancer increases tumour control and overall survival but leads to more severe acute side effects than radiation alone. The influence on severe late side effects is unknown.
- Neo-adjuvant chemotherapy increases tumour control but does not significantly influence the overall survival or risk for distant metastases.

Radiotherapy – dose, fractionation schedule

Overview 2 (after the list of references)

The generally accepted standard fractionation is 1.8–2 Gy/fraction, 5 fractions/week to a total dose of 66–70 Gy in an overall treatment time of 6.5–7 weeks. Altered fractionation has been a focus of interest as a means of increasing the tumouricidal effect of radiation. Generally, three different approaches can be defined

Hyperfractionated radiotherapy (HRT):

Increasing the number of fractions and total dose can be made by using smaller fraction size and more than one fraction per day in the same overall treatment time. The primary aim is to increase the tumour control by the higher total dose while keeping the severe late radiation side effects at a low level by using small fraction sizes. The small fraction size is also considered to give less sparing of hypoxic tumour cells than conventional fraction sizes.

In the previous SBU-report 129/2, hyperfractionation was considered to have a potential for better treatment results. Only one large randomized study was available at that time. Since then two large studies have been reported [16,39]. One study is a very early report and indicates that hyperfractionation improves locoregional control but not survival [16]. The improvement is accompanied by increased acute side effects and in [39] also late side effects. In [39] 3 fractions per day are delivered with only four hours interval. Today this is generally believed to be a too short interval to allow full repair of sublethal DNA damage.

Accelerated radiotherapy (ART):

Shortening of overall treatment time can be made by using more than five fractions per week. The dose per fraction is usually conventional or marginally lower than that in conventional radiotherapy. The total dose is often similar to conventional. The primary aim is to overcome tumour cell proliferation during radiotherapy and thereby increase the effectiveness of radiation. Slowly proliferating tissues, such as late reacting normal tissues, are generally assumed to be less sensitive than tumours to changes in overall treatment time.

This fractionation is represented by four studies [16,19,34,38]. In [16] two groups with different types of accelerated fractionation are compared with conventional fractionation. In [38] where only nasopharyngeal cancers are included, the controls are not treated conventionally. The six weeks concomitant boost technique of [16] and the five (to six) weeks techniques of [19] and [34] all demonstrated a significantly better locoregional control compared with conventional therapy. However, both the acute and severe late toxicity were significantly increased [19,34]. In the concomitant boost treatment there was no evidence of increased severe late side effects but the follow-up is too short for firm conclusions [16]. The accelerated therapy with a split course did not show any advantage over conventional therapy with respect to tumour control [16]. An accelerated schedule used for nasopharyngeal cancer proved to be more toxic to nervous system than a slower fractionation [38].

Hyperfractionated accelerated radiotherapy (HART):

This is a combination of the two previously described fractionations were the overall treatment time is usually shorter than that of accelerated radiotherapy and the total dose is lower than that of conventional therapy. The aim is to more effectively overcome tumour cell proliferation and thereby "sparing" dose to slowly proliferating normal tissues.

Two studies have been published using similar fractionation [11,12]. Neither shows any improved tumour control. The large study with a long follow-up shows a significant reduction in severe late side effects while the acute effects are worse [11]. Quality of life assessments did not show any clear difference between patients treated conventionally

or with accelerated hyperfractionation [17]. The cost per patient for the accelerated therapy was approximately GBP 1000 higher than that of the conventional [10].

The literature shows that:

- Altered fractionation often results in worse acute side effects compared with conventional.
- Hyperfractionated radiotherapy may increase locoregional tumour control without increasing severe late side effects but the interfraction interval is important.
- Accelerated radiotherapy may increase locoregional tumour control without increasing severe late side effects but the type of fractionation schedule is important for the outcome.
- Accelerated hyperfractionation has a similar tumour control rate compared with conventional and a lower incidence of severe late side effects. The cost of radiotherapy is higher with CHART (Continuous hyperfractionated accelerated radiotherapy).
- Neural tissues might be more susceptible to radiation damage from altered fractionation than from conventional.

Radiotherapy – prophylactic treatment of side effects

Overview 3 (after the list of references)

The prevention of severe acute and/or late side effects is the subject of many publications. Only few report patient numbers that are large enough for drawing meaningful conclusions about the effectiveness of therapy [5,15,25,28,30,35,36,40,42]. Sucralfate was administered with the aim of reducing acute mucositis [5,15,25,28,30,35,36,40,42]. No clear evidence for symptom relief can be identified. The effect of local treatment with tobramycin, polymyxin E and amphotericin B have been investigated [30,36]. The results are heterogeneous, probably partly as a consequence of different end points. In two reports some subjective relief from mucositis could be detected while no effect could be found in one. One study also identified an objective effect on the area of mucosa with confluent mucositis. In one study G-CSF was evaluated as an agent to reduce

mucositis [35]. A very early report from this study indicates significantly worse locoregional control in patients treated with G-CSF.

Amifostine is a radical scavenger. It is therefore a radioprotective substance. One study addressing the ability of amifostine to selectively protect normal tissues in radiotherapy of head and neck tumours has been published (in two articles) [5,40]. The patient material is heterogeneous and the number of patients is comparatively small which leads to a low statistical power for detecting differences in tumour control. The majority of randomized patients (199/303) were treated with radiotherapy postoperatively. The clinical significance of the difference in xerostomia between groups by patients' assessment is hard to interpret due to the way the data is presented. There are no dose-volume relationships reported to facilitate the possibility of quantifying the change in response to radiation of the parotids. The incidence of grade ≥2 acute and late xerostomia by doctors' assessment showed a statistically significant reduction. These end points will be influenced not only by the inclusion of parotid glands in the radiation fields but also the other large salivary glands and the auxiliary salivary glands. Data on these issues are not clearly reported. There was no difference in incidence in high grade mucositis between groups. Neither was there any statistically significant effect on locoregional control. The side effects from the drug were not negligible. Other studies performed in order to evaluate amifostine were excluded due to the criteria that were set up in the overview.

The literature shows that:

- Sucralfate has no role as a prophylactic agent against acute or late side effects in the radiotherapy of head and neck cancers.
- Local therapy with tobramycin, polymyxin B and amphotericin B may reduce acute radiation induced mucositis slightly.
- The use of G-CSF for reducing mucositis is poorly evaluated but it should be noted, that a reduced locoregional tumour control has been observed.
- Amifostine partially protects parotid glands from radiation effects. The existence or magnitude of any tumour protection can not be evaluated from existing data.

Radiotherapy – hypoxic cell sensitizers

Overview 4 (after the list of references)

Four large studies on hypoxic cell sensitizers have been published since the previous report [14,22,31,39]. Nitroimidazole derivatives are used for sensitization in all studies. Three studies show no effect on tumour control or survival from the sensitizer. One study showed better locoregional control with nimorazole treatment during the course of radiotherapy [31]. This study included patients with pharyngeal tumours and tumours of the supraglottic larynx. Nimorazole seems to be the least toxic of the drugs tested. The results of this trial may be confounded by an imbalance between the patient groups. The control group had more stage IV tumours than the intervention group. However, in this study a less heterogeneous group of patients was included compared with the three other studies. This group of patients had been identified in a previous subgroup analysis of another study.

The literature shows that:

- Three out of four studies fail to show a statistically significant improvement of tumour control by combining radiotherapy with a nitroimidazole derivative.
- One study shows that the nitroimidazole derivative nimorazole increases locoregional control in cancers of the pharynx and supraglottic larynx without increasing toxicity.

Radiotherapy – miscellaneous studies

Overview 5 (after the list of references)

In one study involving 169 patients with head and neck cancers neutron radiotherapy was compared to photon radiotherapy [27]. The tumour control was similar in the neutron treated patients compared with those conventionally treated. Severe late side effects were significantly more common in the neutron treated patients.

In one study patients with supraglottic carcinomas received 40 Gy with conventional fractionation as preoperative radiotherapy or surgery alone

[43]. The reduction of the frequency of locoregional recurrences was not statistically significant. This might reflect an insufficient radiation dose in this situation.

The reduction of field size from 6 x 6 to 5 x 5 cm^2 in the treatment of glottic carcinomas with opposed beams, resulted in a significant reduction of late laryngeal oedema and polypoid lesions [7]. The tumour control was similar in both groups. This indicates the importance of reducing the treated of volumes whenever considered possible.

The literature shows that:

- For the same tumour control, neutrons lead to more severe late radiation side effects.
- In preoperative radiotherapy, 40 Gy, delivered with conventional fractionation, might be suboptimal.
- Even moderate changes in the treated volume of normal tissues may significantly influence the risk of late side effects.

Literature

This report is based on 43 scientific articles. One is a meta-analysis, 41 are randomized trials and one is an economical analysis of a randomized trial. The total number of patients is 20 893.

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients).*

	1 = High	2 = Moderate	3 = Low	Total
M	–	1/12 204	–	**1/12 204**
C	2/1 418	12/4 835	25/4 603	**39/8 689**
Total	**2/1 418**	**13/16 616**	**25/2 859**	**40/20 893**

* Since some patients can be included in several reports, the sums of the total are lower than the sums of the numbers given within the table.

Conclusions and comments

Combination of chemotherapy and radiotherapy

General, non-nasopharynx

- Substantial evidence supports that the tumour effect of radiotherapy can be increased by the concomitant administration of chemotherapeutic agents, particularly cisplatin and 5-fluorouracil. ([33]M2, [1]C3, [4]C3, [6]C3, [12]C3, [18]C3, [20]C3, [21]C3, [29]C3, [35]C2, [41]C3).
- There is moderate evidence of a survival benefit of radiation combined with concomitant chemotherapy compared to radiation alone. However, the results are equivocal. ([33]M2, [4]C3, [6]C3, [12]C3, [20]C3).
- There is substantial evidence in published studies for an increased frequency of severe acute side effects as a result of concomitant chemotherapy and radiotherapy. ([1]C3, [4]C3, [6]C3, [12]C3, [35]C2, [41]C3).
- There is an almost complete lack of studies that allow any estimates of the risk for serious late side effects. There is a weak indication of an increased risk for serious fibrosis. ([6]C3).

Comment: The general quality of studies and the lack of information on serious side effects indicate a need for large, well designed, clinical studies with a reasonable follow-up.

Larynx preservation studies

- There is strong evidence that larynx preservation is possible in 50 per cent of the patients surviving for five years with hypopharyngeal cancers when treated with neo-adjuvant chemotherapy and radical radiotherapy. ([33]M2, [23]C3).
- There is a non-significant trend for the overall survival being lower in non-surgically treated patients than in those treated with primary surgery and post-operative radiotherapy. ([33]M2).

Nasopharynx

- There is moderate evidence that patients with nasopharyngeal carcinomas, of the endemic type benefit from therapy with a combination of chemotherapy and radical radiotherapy. However, the results from the reported studies are equivocal. ([2]C3, [3]C3, [8]C3, [9]C3, [26]C2).
- There is some indication that the acute side radiation effects are more severe in the concomitant setting ([2]C3) than in the neoadjuvant. ([3]C3, [8]C3, [9]C3, [26]C2).

Comment: There is no data on serious late toxicity

Dose, fractionation schedules

- There is some evidence that certain schedules of altered fractionation improve tumour control without increasing severe late side effects. ([16]C2).
- There is some evidence that nervous tissues are more susceptible to damage by altered fractionation. ([38]C2).
- Solid data shows that altered fractionation increases acute side effects. ([11]C1, [16]C1, [19]C1, [34]C3, [38]C2, [39]C2).
- There is moderate evidence that accelerated hyperfractionation may reduce the frequency of serious late side effects while retaining a similar tumour effect as conventional radiotherapy. ([11]C1).

Hypoxic cell sensitizers

- A majority of reported trials speaks against the usefulness of nitroimidazole derivatives for sensitization of hypoxic tumour cells. ([14]C2, [22]C2, [39]C2).
- There is some evidence that patients with tumours in the pharynx and larynx may benefit from sensitization by nimorazole. ([31]C2).

Prophylactic treatment of side effects

- There is weak evidence that local antibiotics have a clinically significant effect in preventing acute radiotherapy side effects. ([30]C3, [36]C2, [42]C3).
- There is insufficient evidence that radioprotective agents offer clinically significant protection of parotid glands. ([5]C3, [40]C3) (one study in two publications).
- There is insufficient evidence that radioprotective agents do not spare tumour tissue. ([5]C3, [40]C3) (one study in two publications).

Since the previous report no randomized studies comparing the effectiveness of external beam radiotherapy and brachytherapy have been performed. Both methods are well established and have independently proven to be effective in the treatment of certain head and neck cancers. No conclusion can be drawn regarding their relative effectiveness.

Since the previous report no data to guide the use of intraoperative radiotherapy has been identified.

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Overview 1 *Head and neck cancer. Combination of chemotherapy and radiotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Adelstein 2000 [1] C SC	OS at 3 years with CHT co; **A:** RT 1.8–2.0 Gy/fr, 66–72 Gy/7 w **B:** Same RT + CHT Surgery for "nonresponders" after 55 Gy and as salvage. B 50 pts	1990–1995 Resectable SCC, oral, oroph., hypoph., larynx. St III–IV, M0. A 50 pts
Al-Sarraf 1998 [2] C MC	OS and PFS with CHT co **A:** RT 1.8–2.0 Gy/fr, 70 Gy/7–8 w **B:** Same RT + CHT	1989–1995 Nasoph. ca WHO grade 1–3 St III–IV, M0. 147/193 pat evaluable A 69 pts B 78 pts
Anonymous 1996 [3] C MC	OS and DFS with CHT, neoadj **A:** RT 2.0 Gy/fr, 65–70 Gy/ 6.5–7.5 w **B:** CHT + same RT	1989–1993 Nasoph. Ca WHO grade 2–3 St IV, M0 (N ≥2) A 168 pts B 171 pts

Adj: adjuvant; CHT: chemotherapy; CI: confidence interval; CSS: cause specific survival; co: concomitant; d: day(s); DFS: disease free survival; DMFS: distant metastases free survival; EFS: event free survival; f: fraction(s); HART: hyperfractionated accelerated radiotherapy; HRD: hazard ratio of death; LRC: locoregional control; LRFS: local recurrence free survival; LRPFS: locoregional progression free survival; m: month(s); MC: multi-centre; neoadj: neoadjuvant; NR: not reported; ns: not significant; OS: overall survival; PFS: progression free survival; PRF: progression free; PSP: primary site preservation; pts: patients; QA: quality assurance; RFS: relapse free survival; RRFS: regional recurrence free survival; RT: radiotherapy; SC: single-centre; SCC: squamous cell carcinoma; sign: significant; SLC: survival with local control; surg: surgery; TDF: time-dose factor; tox: toxicity; TRM: treatment related mortality; UNCT: undifferentiated cancer of nasopharyngeal type; w: weeek(s); y: year(s)

CHT ref [1]: Cisplatin 20 mg/m^2, d 1 and 22, + 5-Fu, 1000 mg/m^2, d 1–4 and 22–25 during RT.

CHT ref [2]: Cisplatin 100 mg/m^2, 3 times during RT. Cisplatin 80 mg/m^2, d 1, + 5-Fu 1000 mg/m^2, d 1–5, 3 courses adj after RT.

CHT ref [3]: Bleomycin 15 mg iv push d 1, 12 mg/m^2 continuously inf d 1–5, cisplatin 100 mg/m^2 d 1, epirubicin 70 mg/m^2 d 1. 3 cykles before RT.

Results	Conclusion/Comments
Follow-up median 5 (3–8) y **OS%, at 5 y** A 48 B 50 ns	Surgical intervention in non responders after 55 Gy, numbers not reported. OS with PSP at 3 y and LRC without surgery at 5 y sign better in arm B (p=0.004 and p=0.001) Sign worse acute side effects in group B. Late radiation side effects not possible to evaluate. Late hypothyreosis or secondary malignancy not sign. different between groups. Poor description of RT. No QA of RT stated. Limited by small size. **C3**
Follow-up median 2.7 y **OS%** **PFS%, at 3 y** A 47 26 B 78 63 p=0.005 p=0.001	Early closure of study due to sign diff at planned interim analysis. Small study. Short follow-up (33% < 2 y). 63% received concomitant and 55% adj CHT according to protocol. More severe acute side effects group B. Late side effects not reported. No QA of RT stated. **C3**
Follow-up median 49 (23–70) m **OS%** **DFS%, at 49m** **TRM%** A 44 45.3 1 B 5 0 67.3 8 ns p<0.01 p<0.01	Preliminary report with short follow-up. No later report has been identified. Severe CHT related acute side effects frequent in group B. RT related acute side effects similar in groups. Late effects poorly evaluated. **C3**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Brizel 1998 [4] C SC	Benefit of CHT, co + adj **A:** RT 1.25 Gy/fr, 2 f/d, 75 Gy/6 w **B:** Same RT, 70 Gy/6 w, 1 w split, + CHT	1990–1995 SCC, all sites T3–4, any N, M0. For base of tongue also T2. A 60 pts B 56 pts
Calais 1999 [6] C MC	OS and DFS with CHT, co **A:** RT 2.0 Gy/fr, 70 Gy/7 w **B:** Same RT + CHT	1994–1997 SCC, oroph. St III–IV, M0 A 113 pts B 109 pts
Chua 1998 [9] C MC	OS and RFS with CHT neoadj **A:** RT 2.0–3.5 Gy/fr, 3–5 f/w, 66–74 Gy (calculated by TDF) **B:** CHT + same RT	1989–1993 Nasoph. ca. WHO gr 2–3 Ho st III–IV 286/332 pts evaluable A 152 pts B 134 pts

CHT ref [4]: Cisplatin 12 mg/m^2/d + 5-Fu 600 mg/m^2/d, d 1–5. 2 cycles co, 2 cycles adj.
CHT ref [6]: Carboplatin 70 mg/m^2/d + 5-Fu 600 mg/m^2/d, d 1–4. 3 cycles, w 1, 3, 6 during RT.
CHT ref [9]: Cisplatin 60 mg/m^2 + epirubicin 110 mg/m^2 d 1, every 3rd w x 2–3.

Results	Conclusion/Comments
Follow-up median 41 (19–86) m **OS%** **LRC%, at 3 y** A 35 44 B 55 70 ns p=0.01	No. of pts with N2–3 higher in A, 63% vs. 44% in B (ns). A greater proportion of pts had elective neck node dissection in group B. Nearly all pts received CHT co as scheduled, only 57% received CHT adj. Acute side effects worse in group B (one death in sepsis). Severe late toxicity (soft tissue or bone necrosis) 9 pts in group A vs. 11 in group B (ns). Small study with short follow-up. **C3**
Follow-up median 35 (12–56) m **OS%** **DFS%, at 3 y** A 31 20 B 51 42 p=0.02 p=0.04 Overall late tox (grade 3–4) at the time of analysis was 9% in A, 14% in B. Trend for higher incidence of severe cervical fibrosis in B (p=0.08). No cases of bone necrosis.	Worse acute side effects in group B, confluent mucositis, moist dermatitis, tube feeding twice as frequent. Short follow-up. **C3**
Follow-up median 41 (5–77) m **OS%** **RFS%, at 3 y** A 71 42 B 78 ns 48 ns	Preliminary result; final results from one of the centres published later [8]. 5% in group A, 14% in group B didn't receive planned RT. RT varied between centers. Total dose not reported, calculated by TDF. Treatment time not reported. Description of RT and QA are lacking. RT not conventional. **C3**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Chua 2001 [8] C SC	Report from one center participating in ref 9 study. **A:** RT 3,5 Gy/fr, 3f/w, 59.5 Gy (limited tumours) RT 2.5 Gy/fr, 4f/w, 40 Gy + 3,5 Gy/fr, 3f/w, 21 Gy/2 w (extensive tumours) **B:** same RT + CHT ref. 9	Subgroups of patients in ref [9] A 87 pts B 92 pts
Dobrowsky 2000 [12] C SC	OS with HART and CHT co **A:** 2.0 Gy/fr, 70 Gy/7W **B:** 2.5 Gy 1st f + 1.65 Gy/fr, 2 f/d, 14 f/w, 55.3 Gy/17 d (V-CHART) **C:** RT V-CHART + CHT	1990–1997 SCC, oral, oroph., hypoph., larynx St II–IV, M0 A 81 pts B 78 pts C 80 pts
Domenge 2000 [13] C MC Included in meta-analysis ref. [33]	OS with CHT neoadj **A:** RT 2.0 Gy/fr, 70 Gy/7 w (no surg) 65 Gy/6.6 w (non radical surg) 50 Gy/5 w (radical surg) **B:** CHT + same RT	1986–1992 SCC, oroph., T2–4, N0–2b, M0 A 161 pts B 157 pts
Haffty 1997 [18] C SC Included in meta-analysis ref. [33]	"Improved outcome" of CHT co **A:** 2.0 Gy/fr, 60 Gy/6 w (if pre or postop). 68 Gy/7 w (if no surg) **B:** Same RT + CHT **C:** Same RT + CHT + dicumarol Data pooled from 2 trials: 1. A vs B 2. A vs C	Trial 1: 1980–86 Trial 2: 1986–92 SCC, oral, oroph., hypoph, larynx, nasoph, sinus, unknown. St I–IV and recurrent, M0 A 104 pts B 56 pts C 35 pts

CHT ref [12]: Mitomycin C 20 mg/m^2 on d 5 of RT.
CHT ref [13]: Cisplatin 100 mg/m^2 d 1, + 5-Fu 1000 mg/m^2, d 1–5, 2–3 cycles before RT.
CHT ref [18]: Group B: Mitomycin C 15 mg/m^2 d 5 and also week 6 if RT >60 Gy.
Group C: Mitomycin as gr B + dicumarol 300 mg d 4, 200 mg d 5.

Results	Conclusion/Comments
Follow-up median 96 (8–121) m **OS% RFS%, at 5 y** A 67 42 B 70 ns 53 ns	If parapharyngeal spread or lymphnodes, still palpable at end of RT, a boost of 10.5 Gy/3 fr was given. Not standard RT. Small pts material. Poor QA of RT. Acute gr. 2–3 mucositis 16% in A vs. 21% in B (ns). Late side effects not reported. DMFS 68% in A vs. 70% in B at 5 y (ns). **C3**
Follow-up median 4 y (range NR) **OS%, at 4 y** A 18 B 18 C 32 p=0.03	Worse acute side effects in group B and C. Hematological toxicity grade 3–4 18% in group C. Crude LRC shows a similar pattern as OS. Small number of pts. QA and late side effects not reported. **C3**
Follow-up median 5 y (range NR) **OS%** A 40 B 50 p=0.03 (hazard ratio 0.71 (0.40–1.02) No sign diff in EFS	The trial closed prematurely, slow inclusion. Heterogeneously treated pts. Description of RT and QA poor. Acute and late side effects of RT not reported. **C3**
Follow-up median 11.5 y (8 m–15.5 y) **OS% CSS% LRC%, at 5 y** A: 42 48 54 B,C 48 ns 74 76 p=0.005 p=0.003 No difference in non-haematological acute tox.	Heterogeneous trials. Small material. Large variety of tumours and locoregional treatments. Description of RT and QA poor. Dicumarol did not seem to have an additional effect. Late side effects poorly reported. **C3**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Jeremic 1997 [21] C SC Included in meta-analysis ref. [33]	OS with CHT co **A:** RT 1.8–2.0 Gy/fr, 70 Gy/7–7.5 w **B:** Same RT + CHT[1] **C:** Same RT + CHT[2]	1988–1990 SCC oral, oroph., hypoph., larynx, nasoph. Unresectable, stage III–IV, M0 A 53 pts B 53 pts C 53 pts
Jeremic 2000 [20] C SC	OS with CHT co **A:** 1.1 Gy/fr, 2 f/d, 77 Gy/7 w **B:** Same RT + CHT	1991–1993 SCC oral, oroph., hypoph., larynx, nasoph. St III–IV, M0 A 65 pts B 65 pts
Lefebvre 1996 [23] C MC Included in meta-analysis ref. [33]	OS, DFS, larynx preservation with CHT neoadj and RT vs surgery and RT. **A:** 1) surg + postop RT 2.0 Gy/fr, 50 Gy 2) if pos surg margin to 64 Gy **B:** CHT + 1) if CR – RT 2.0 Gy/fr, 70 Gy 2) if <CR – op + RT as in gr A	1990–1993 SCC, pyriform sinus, aryepiglottic fold. St II–IV, N <2c, M0. A 94 pts B 100 pts

CHT ref [21]: CHT[1] Group B: Cisplatin 6 mg/m^2/d during RT. CHT2 Group C: Carboplatin 25 mg/m^2/d during RT.
CHT ref [20]: Cisplatin 6 mg/m^2/d during RT
CHT ref [23]: Cisplatin 100 mg/m^2 d 1, 5-Fu 1000 mg/m^2 d 1–5, 2–3 cycles before RT.

Results	Conclusion/Comments
Follow-up NR **OS%** **LRFS%** **RRFS%** A 5 27 70 B 32 51 72 C 31 48 74 A vs B p=0.011 p=0.018 ns A vs C p=0.019 p=0.04 ns B vs C ns ns ns No sign diff in acute RT related side effects between groups.	Difference in DMFS at 5 y ns. The stated numbers on late effects cannot be evaluated in detail from the article since the time of assessment and number of patients at risk are not reported. Small study. Length of follow-up not stated. The type of randomization procedure not stated. No QA of RT. Description of RT poor. **C3**
Follow-up median 79 m **OS%** **LRPFS%** **DMFS%, at 5 y** A 25 36 57 B 46 50 86 p=0.008 p=0.04 p=0.001 No statistically sign. diff in acute RT related tox (gr >3) or late effects (gr >3)	Randomization procedure is not stated. No QA of RT. Description of RT poor. Small study. DMFS in group A lower than usually expected with regard to the tumour types included. The reported late effects cannot be evaluated in detail from the article since the time of assessment and number of patients at risk are not reported. **C3**
Follow-up median 51 (3–106) m **OS%** **DFS%** **OS%, at 3 y with PSP** A 43 25 0 B 57 ns 43 ns 28 (95% CI 17–37)	QA of RT not stated. No conclusion can be drawn regarding the effectiveness of RT alone vs the combination of RT and CHT. The size of the study does not allow firm conclusions on differences in survival. **C3**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Lewin 1997 [24] C MC Included in meta-analysis ref. [33]	OS with CHT neoadj **A:** RT 2.0 Gy/fr, 64–70 Gy/6,5–7 w **B:** CHT + same RT	1986–1991 SCC, oral, oroph., hypoph., larynx. St II–IV, M0 A 228 pts B 233 pts
Ma 2001 [26] C SC	OS with CHT neoadj **A:** RT 2.0 Gy/fr, 68–72 Gy/7 w + boosts (varying techniques) if bone involvement and/or residual tumour. **B:** CHT + same RT	1993–1994 Nasoph. ca 97% WHO grade II–III. Stage III–IV, M0 (Chinese 1992 staging). A 225 pts B 224 pts
Merlano 1996 [29] C Included in meta-analysis ref. [33]	OS with CHT co **A:** RT 2.0 Gy/fr, 70 Gy/7 w **B:** RT 2.0 Gy/fr, 60 Gy/9 w, 2 splits + CHT RT w 2–3, 5–6, 8–9 CHT w 1, 4, 7, 10	1987–1990 SCC or UNCT, oral, oroph., hypoph., larynx, nasoph. St III–IV, M0 A 77 pts B 80 pts
Paccagnella 1994 [32] C MC Included in meta-analysis ref. [33]	OS with CHT neoadj **A:** RT 2.0 Gy/fr, 45–50 Gy/ 4.5–5 w if post-op RT 2.0 Gy/fr, 65–70 Gy/6.5–7 w if no surgery. 2 w split allowed **B:** CHT + same RT	1986–1990 SCC, oral, oroph., hypoph., sinus Stage III–IV, M0 Age <70 y A 119 pts B 118 pts

CHT ref [24]: Cisplatin 100 mg/m^2 d 1, 5-Fu 1000 mg/m^2 d 1–5, 3 cycles before RT.
CHT ref [26]: Cisplatin 100 mg/m^2 d 1, bleomycin 10 mg/m^2 d 1, 5-Fu 1000 mg/m^2 d 1–5, 2–3 cycles before RT.
CHT ref [29]: Cisplatin 20 mg/m^2 + 5-Fu 200 mg/m^2 d 1–5 between RT weeks.
CHT ref [32]: Cisplatin 100 mg/m^2 d 1, 5-Fu 1000 mg/m^2 d 1–5 every 3rd w, 4 cycles before RT.

Results	Conclusion/Comments
Follow-up median 4.5 (1.5–8) y **OS%, at 3 y** A 30 B 32 ns CHT related toxicity gr >3 16%. 5 treatment related deaths in B.	RT doses and volumes are poorly reported. QA procedures not reported. Acute and late RT side effects not reported. **C2**
Follow-up median 5.5 (3–6) y **OS%** **RFS%** **DMFS% at 5 y** A 56 49 75 B 63 ns 59 79 ns p=0.05 Acute RT related side effects similar in the groups.	Randomization procedure NR. No QA procedure reported. Late tox NR. **C2**
OS% **LRC%** **PRF%, at 5 y** A 10 32 9 B 24 64 21 p=0.01 p=0.04 p=0.008 Acute RT related toxicity reported to be similar in A and B.	Low compliance to protocol in group A (mean target dose was 65 Gy). QA NR. Late side effects NR. Small study. Study closed prematurely, due to poor accrual "once a higher percentage of complete responses was observed with the combined treatment". Very poor survival in group A. **C3**
Follow-up minimum 2 y **OS%** **DFS%, at 3 y** A 20 33 B 29 ns 37 ns DMFS sign longer for group B, p=0.002	RT poorly reported. No QA procedure reported. Acute and late side effects not reported. Subgroup analysis shows higher OS for inoperable pts in group B (p=0.04). **C3**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Pignon 2000 [33] M	OS at 2 and 5 y with: **I:** Locoregional treatment +/– CHT **II:** Neoadj CHT vs. concomitant or alternating CHT **III:** Radical surgery and RT vs. neoadj CHT and radical RT and salvage surgery for larynx preservation	RCT studying SCC of H&N, M0, starting after 65-01-01 and ended before 93-12-31. Those studying nasoph. ca alone were excluded. The investigator had to be unaware of the assigned treatment before deciding eligibility **I:** 63 trials, 10 741 pts **II:** 6 trials, 861 pts **III:** 3 trials, 602 pts

Results	Conclusion/Comments
Follow-up was individually updated, specifically for the meta-analysis. Median follow-up 5.9 y **I** **CHT: Effect on OS** Total HRD (95% CI): 0.90 (0.85–0.94) (p<0.0001) corresponding to absolute survival benefit of 4% at 2 and 5 y. Heterogeneity of results (p<0.0001). Subgroups **Adj CHT** HRD: 0.98 (0.85–1.19) ns, corresponding benefit in OS at 2 and 5 y, 1%. Heterogeneity, ns. **Neoadj CHT** HRD: 0.95 (0.88–1.01) ns, corresponding to absolute survival benefit of 2% at 2 and 5 y. Heterogeneity, ns. **Concomitant CHT** HRD: 0.81 (0.76–0.88) (p<0.0001), corresponding absolute benefit in OS at 2 and 5 y, 7% and 8%. Heterogeneity of results (p<0.0001). See comment! **II** HRD was 0.91 (0.79–1.06) ns, in favour of alternating or co CHT. Heterogeneity was ns. **III** HRD was 1.19 (0.97–1.46) ns, in favour of primary surgery. Significant heterogeneity (p=0.05)	Follow-up is adequate No analysis of severe (early and) late side effects. As a consequence, the results cannot distinguish a tumour-specific, radiosensitizing effect of chemotherapy from a pure dose-modifying factor leading to better tumour control accompanied by a higher frequency of severe side effects. The effects on survival are smaller than in most individually published studies. **I:** The benefit for the co CHT came from 14 trials with 11% of the patients prohibiting firm conclusions about the absolute benefit of co CHT. The trials were divided in two groups, one with conventional radiotherapy and same dose in both arms (12 trials, 2516 pat). In this group the HRD was 0.89 (95% CI: 0.81–0.97). The second group included trials with surgery as part of initial therapy, prolonged treatment times, lower RT doses etc. They showed a larger effect of concomitant chemo than the group with conventional radiotherapy as control. Multi-agent concomitant chemotherapy was compared with single agent. The most benefit was seen in the multi-agent group. Further subgroup analysis showed significant effect in neoadjuvant trials for those where CHT was cisplatin and 5-FU (15 trials, 2487 pat) with HRD 0.88 (95% CI: 0.79–0.97). **II:** No statistically sign effect of timing of CHT could be detected. **III:** There is not significant neg. effect on OS of larynx preservation. The role of CHT can not be determined. **M2**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Staar 2001 [35] C MC	CHT co **A:** RT 1.8 Gy/fr, 5 f/w in 5.5 w + boost: 1.8 Gy + 1.5 Gy/d, 10 f/w in 2.5 w, 69.9 Gy in 38 d **B:** Same RT + CHT Both groups randomized to ± G-CSF d 15–19	1995–1999 SCC, oroph., hypoph. Unresectable, st III–IV, M0 A 127 pts B 113 pts
Taylor 1994 [37] C MC Included in meta-analysis ref. [33]	OS and PFS with CHT neoadj vs co **A:** CHT + RT 1.8–2.0 Gy/fr, 70 Gy/7w, in some pts surgery before RT **B:** RT, 2.0 Gy/fr, 5f/w, every 2nd w, 70 Gy/13 w + CHT co	1986 –1991 SCC, oral, oroph., larynx, St IV, M0 Sinus, tongue, nasoph., hypoph., St III–IV, M0 Unresectable A 107 pts B 107 pts
Wendt 1998 [41] C MC Included in meta-analysis ref. [33]	OS with CHT co **A:** RT 1.8 Gy/fr, 1–2 f/d, 6–8 f/w to 70.2 Gy/8 w, 11 d splits after 15 f and 28 f **B:** Same RT + CHT	1989 –1993 SCC, oral, oroph., hypoph., larynx. St III–IV, M0 A 140 pts B 130 pts

CHT ref [35]: Carboplatin 70 mg/m^2 and 5-Fu 600 mg/m^2 d 1–5, 2 cycles during w 1 and 5 during RT.
CHT ref [37]: A: Cisplatin 100 mg/m^2 d 1, 5-Fu 1000 mg/m^2 d 1–5, every 3rd w, 3 cycles before RT.
B: Cisplatin 60 mg/m^2 d 1, 5-Fu 600 mg/m^2 d 1–5, every 2nd w, 7 cycles during RT.
CHT ref [41]: Cisplatin 60 mg/m^2 + 5-Fu 350 mg/m^2 + leukovorin 50 mg/m^2 d 2–4, 3 cycles, started d 2, 22 and 44 during RT.

Results	Conclusion/Comments
Follow-up median 22 (6–53) m **LRC% SLC%, at 1y/2y** A 58/45 44/32 B 69/51 ns 58/38 p=0.05/ns LRC sign worse in G-CSF treated pts (p=0.007). Sign more mucositis gr >3 in B. Continuous tube feeding needed in 25% in A vs 51% in B.	Early report of a study with a 2^2-design. No QA procedure reported. No statistically sign difference in LRC found between A and B. Acute side effects sign worse in B. Follow-up too short for meaningful analysis of late effects. Possible negative effect of adding G-CSF. **C2**
Follow-up median 30 (<24–?) m **OS% PFS%, at 21 m** A ~47 33 B ~47 ns 46 ns Weight loss more severe in B (p=0.02). 6 pts died during treatment in A vs. 11 in B (ns). Haematological tox more severe in B (p=0.04). Mucositis similar in both arms. Incidence of distant metastases 10% in A vs 7% (ns).	Short follow-up (15% <2 y). No QA reported. RT poorly described. OS estimated from fig. in article. The groups differ with respect to RT schedules and surgery for some pts in group A. These factors may confound any CHT effects. Late side effects not reported. QoL assessment performed but not reported. **C3**
Follow-up NR **OS% LRC%, at 3 y** A 25 17 B 49 35 p<0.0003 p<0.004 Mucositis, dermatitis gr >3 worse in B. (p<0.001, p<0.05) Severe late effects 6.4% A, 10% in B (ns). Incidence of distant metastases similar in A and B.	No QA reported. Unconventional, suboptimal treatment in group A. Poor survival in group A and a high rate of severe late side effects in group B. The reported late effects cannot be evaluated in detail from the article since the time of assessment and number of patients at risk are not reported. **C3**

Overview 2 *Head and neck cancer. Radiotherapy – dose, fractionation schedule.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Dische 1997 [11] C MC	LRC with HART **A:** 2.0 Gy/fr to 66 Gy/6.5–7 w **B:** 1.5 Gy/fr, 3 f/d (6 h interval) 21 f/w, 54 Gy/12 d	1990–1995 SCC, oral, oroph., hypoph., larynx. St II–IV, M0, and sinus, nasoph., St I–IV, M0 A 366 pts B 522 pts
Coyle 1997 [10] Economical analysis of study ref. [11]	Cost analysis of treatment in ref. [11]	Same pts as in ref. [11]
Griffiths 1999 [17] C QoL effects in study ref. [11]	Analysis of QoL in ref. [11]	Same pts as in ref. [11]

ART: Accelerated radiotherapy; CB=concomitant boost, CRT: conventionally fractionated radiotherapy; CSS: cause specific survival; d: day; DFS: disease free survival; f: fraction(s); h: hour(s); HART: hyperfractionated accelerated radiotherapy; HRT: hyperfractionated radiotherapy; LRC = locoregional control; m: months; MC: multi-centre; NR: not reported; ns: not significant; pts: patient(s); OS: overall survival; QA: quality assurance; QoL: quality of life; RFS: relapse free survival; RT: radiotherapy; SC: single-centre; SCC: squamous cell carcinoma; TRM: treatment related mortality; y: year

Results	Conclusion/Comments
Follow-up median 5 (NR) y **OS%** **LRC%, at 5 y** A 52 53 B 53 ns 55 ns Acute mucositis (gr 2–4) 43% group A, 73% group B. High grade acute skin reaction less frequent in B. Sign NR. Severe late effects less frequent in group B. Osteoradionecrosis in group A 1.4%, in group B 0.4% (sign NR). B showed lower incidence of skin teleangiectasia (p=0.003), moderate-severe fibrosis (p=0.046), mucosal ulceration (p=0.003), dysphagia (p=0.009), and laryngeal oedema (p=0.009).	The same tumour effect was reached with a lower total dose and fewer late side effects. **C1**
Increased costs for HART of £ 1000 per patient	The cost could be reduced by organisational adaptation to this kind of therapy. See ref. [11].
No clear diff in QoL between groups.	The objective benefits regarding late RT side effects could not be detected in QoL. See ref. [11]. **C1**

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Overview 2 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Fu 2000 [16] C MC	LRC with HRT, RT with a split, and CB **A:** 2.0 Gy/fr to 70 Gy/7 w (CRT) **B:** 1.2 Gy/fr, 2 f/d, (6 h apart), 81.6 Gy/7 w (HRT) **C:** 1.6 Gy/fr, 2 f/d, (6 h apart), 67.2 Gy/6 w. 2 w split (ART) **D:** 1.8 Gy/fr, 1 f/d, 30 f/ 6 w; last 12 days boost of 1.5 Gy added 6 h later. Total dose 72 Gy/6 w (CB)	1991–1997 SCC, oral, oroph., supraglottic larynx, St III–IV, M0. Base of tounge, hypoph., St II–IV, M0. A 268 pts B 263 pts C 274 pts D 268 pts
Horiot 1997 [19] C MC	LRC, DFS and late complications of HRT with a split **A:** 1.8–2.0 Gy/fr, 70 Gy/7–8 w **B:** 1.6 Gy/fr, 3 f/d, (4 h apart), 28.8 Gy/18 f / 8 d. Split 12–14 d. Continued HRT, 27 f, 43.2 Gy/17 d. Total dose 72 Gy/5 w (HRT)	1985–1995 SCC, all sites (except hypoph.) T2–4, any N, M0. A 253 pts B 247 pts
Skladowski 2000 [34] C SC	Tox, LRC, and OS of ART **A:** 1.8–2.0 Gy/fr, 5 f/w, 67–76 Gy/7–8 w **B:** 1.8–2.0 Gy/fr, 7 f/w, 67–76 Gy/5–6 w	1993–1996 SCC, oral, oroph., hypoph., supraglottic larynx. T2–4, any N, M0. A 49 pts B 51 pts

Results	Conclusion/Comments
Follow-up median 41 m (range NR) **LRC%, at 2 y** A 46 B 54 p=0.045 C 48 ns D 55 p= 0.05 OS and DFS show no sign difference between groups. B, C, D sign worse acute side effects vs A. No sign diff in late effects.	QA procedure. Early report. Short follow-up. Possible benefit with HRT and CB in LRC to the price of worse acute side effects. Follow-up too short for conclusions on survival and late side effects. **C2**
Follow-up median 4,8 y (7 m–10 y) **LRC%, at 5 y** A 46 B 59 p=0.02 OS and CSS did not show sign difference between A and B. Acute side effects (gr >3) worse in B. Life threatening acute side effects 2% in A vs. 5% in B (p=0.052). Severe late connective tissue damage and severe mucosal sequele sign more common in B (p<0.001 and 0.011). Overall late sequele with major functional damage 4% in A and 14% in B. TRM 6 pts in A, 11 pts in B.	Significant benefit in local control to the price of a high frequency of severe complications in group B. **C1**
Follow-up median 37m (<12–52) m **OS%** **LRC%, at 3 y** A 32 37 B 78 82 p<0.0001 p<0.0001 Acute side effects worse in B. Late side effects worse in B.	Small study with a short follow-up. QA procedure NR. The material heterogeneous as severe side effects lead to reduction of dose/f when about 50% of the pts were included, prolonging treatment time. The difference of 2 w between groups remained after changing the protocol. **C3**

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Overview 2 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Teo 2000 [38] tumour C	OS and LRC of HRT **A:** 2.5 Gy/fr, 4 f/w, 60 Gy/6 w **B:** 2.5 Gy/fr, 4 f/w, 20 Gy followed by 1.6 Gy/fr, 2f/d, (6 h apart), 71.2 Gy/6 w (HRT) Boosts to parapharyngeal spreed and/or residual tumour after RT used in both groups.	1993–1995 Nasoph., T1–3, N <2, M0, (Ho's classif. 1978). Histology or grade NR. A 82 pts B 77 pts
van den Bogaert 1995 [39] C MC	Long term results of HRT with split **A:** 1.7 or 2.0 Gy/fr, 70 or 75 Gy/7 or 9 w (CF) **B:** 1.6 Gy/fr, 3 f/d (4 h apart), 48 Gy. Split 3–4 w. Continued HF RT to total dose 67.2 or 72 Gy/7–8 w (HRT). **C:** RT as B + misonidazole 1 g/m^2, before 1st fraction each day.	1981–1984 SCC, all sites. Stage IV, M0 A 175 pts B 173 pts C 175 pts

Results	Conclusion/Comments
Follow-up median 59 (46–?) m **OS% RFS%, at 5 y** A 87 77 B 85 ns 85 ns Acute side effects similar in the groups. Severe neurological late effects 23% in group A, 49% in group B (p=0.001).	Small study. No QA procedure reported. Unconventional RT in control group A. No better effect with HRT but increased risk for severe neurological side effects. **C2**
Long term results, follow-up NR. **OS% LRC%, at 5 y** A 11 10 B 12 9 C 14 ns 11 ns Acute toxicity worse in B and C groups. One treatment related death in B and 2 in C. Late effects (gr >3).14%, 39%, 41% in A, B, C respectively. Late treatment related deaths; A: 1, B: 2, and C: 10. Significans not reported for side effects.	No obvious effect with misonidazole. No improvement in LRC with HRT or HRT + misonidazole. More acute and late toxicity with misonidazole. **C2**

Overview 3 *Head and neck cancer. Radiotherapy – prophylactic treatment of side effects.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Brizel 2000 [5] C MC	Acute and late xerostomia, mucositis, patients' assessment of benefit, LRC, DFS, OS. **A:** RT 1.8–2.0 Gy/fr, 50*–70** Gy/5-7 w * if post operative (34% of pts), ** if no surgery (66% of pts) **B:** Amif + same RT	1995–1997 SCC, all sites except glottic and salivary gland tumours; RT dose to >75% of parotic glands bilat. >40 Gy. A 150 pts B 153 pts
Franzén 1995 [15] C Double blind SC	Effect on acute mucositis, dysphagia and pain **A:** RT 2.0 Gy/fr, 40–55 Gy/4–5.5 w or 2.0 Gy/fr to 56–66 Gy/5.5–6.5 w **B:** Sucr + same RT	Accrual time NR SCC, all sites. RT with curative intention. A 25 pts B 25 pts
Lievens 1998 [25] C Double blind MC	Effect on acute mucositis, dysphagia RT 2.0–2.2 Gy/fr, 55–60 Gy/w **A:** RT + placebo **B:** RT + sucr 1g x 6/d from 3rd RT w	Accrual time NR SCC, oral 83/102 pts evaluable A 45 pts B 38 pts

Amif=amifostine 200 mg/m^2 iv before each fraction; xero=xerostomia; sucr=sucralfate
ab: antibiotics; BRT: brachytherapy: CF: conventional fractionated; D: day(s); f: fraction(s); m: month(s);
MC: multi-centre; ns: not significant; pts: patient(s); QA: quality assurance; SC: single-centre;
SCC: squamous cell carcinoma; sign: significance; w: weeks;

Results	Conclusion/Comments
Follow-up median 26 m, min 18 m **Xerostomia gr >2 OS% RC%,** **acute,% late,% at 1.5 y** A 78 57 81 68 B 51 34 73 ns 65 ns p<0.0001 p=0.02 Saliva production, >0.1 g unstimulated 49% in A vs. 72% in B (p=0.003) after 1 y. Corresponding results for median quantity was 0.10 g vs 0.26 g (p=0.04). Mucositis gr >3 no sign difference. A patient questionnaire showed a significant difference in favour of amifostine treated (p=0.008). The difference in patients' assessment was 0.70 on a 10 degree scale. The mean score correlated significantly with xerostomia grade (r=0.455, p=0.0001) and saliva production (r=0.304, p=0.0001). Amifostine toxicity included nausea, vomiting, hypotension and allergic reactions. A majority of patients needed antiemetics. 21% discontinued amifostine.	The study shows a statistically significant difference in xerostomia between groups. There is strongly significant correlation between these measures but very low degree of explanation. Only about 9 and 20% of the total variation is explained by the correlation. I.e. using one of these parameters to estimate the other gives a very unreliable result. It is hard to interpret the size of the patient benefit from the results. No effect on mucositis could be detected. No effect on tumour control or survival could be detected. However, the size of the study, the short follow-up and the heterogeneous material give a low power to detect even quite substantial differences. Thus, the statement by the authors that the study argues against a tumour protective effect of amifostine, needs to be questioned. It is not clear how the volume of parotid tissue receiving a certain dose was assessed. It is not stated to what extent other salivary glands as well as accessory salivary glands where included in the treatment volume. Differences between the groups could confound the assessments of xerostomia by the physician and the patient. **C3**
A sign decrease in the proportion of pts with grade 2–3 of mucositis was observed 2–4 weeks after start of sucralfate treatment (p<0.05). Pain and dysphagia ns.	Small study and heterogeneous material. Assessment of volume of irradiated mucosa not clear. No QA of RT reported. **C3**
No significant effects could be detected.	**C2**

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Overview 3 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Meredith 1997 [28] C Double blind SC	Symptomatic effect on acute mucositis RT 1.8 Gy/fr, 5 f/w, >40 Gy to oral cavity, pharynx or oesophagus **A:** RT + placebo **B:** RT + sucr 1g x 6/d	1988–1990 A 58 pts B 53 pts
Okuno 1997 [30] C Double blind MC	Ab effect on acute mucositis assessed by health care provider and by patient RT 1.2–2.2 Gy/fr, >45 Gy or >3.0 Gy/fr, >30 Gy, to >1/3 of oral mucosa **A:** RT + placebo **B:** RT + ab containing drug	1991–1993 A 54 pts B 58 pts
Symonds 1996 [36] C Double blind SC	Ab effect on acute mucositis, pain, dysphagia, weight loss RT: 60–70 Gy; 5 f/w; 6–7 w or, CHART **A:** RT + placebo **B:** RT + ab containing drug	Accrual time NR A 139 pts B 136 pts
Wasserman 2000 [40] C	Patients assessment on the benefit of amifostine treatment during RT. See ref. [5], same study.	See ref. [5], same study.
Wijers 2001 [42] C Double blind SC	Ab effect on mucositis gr 3 after 3 w of RT. RT to 46–70 Gy Some pts treated post op. Some pts got a BRT boost **A:** RT + placebo **B:** RT + ab containing drug	1993–1997 A 38 pts B 39 pts

Ref [30]: ab containing drug=Lozenge containing tobramycin, polymyxin E, amphotericin B.
Ref [36]: ab containing drug=pastilles containing tobramycin, polymyxin E, amphotericin B.
Ref [42]: Drug=oral paste containing tobramycin, polymyxin E, amphotericin B., 1 g x 3/d

Results	Conclusion/Comments
No significant improvement of mucositis symptoms of sucralfate	Heterogeneous material. Assessment of volume of irradiated mucosa not clear. No QA of RT stated. **C3**
Mucositis gr 3–4% **Duration assessed by:** **doctor/nurse** **patient, w** A 1.04 3.7 B 1.31 ns 2.7 p=0.04 The maximum grade of mucositis did not differ between groups whether objective or subjective scoring.	Heterogeneous group. The authors state that "the magnitude of benefit appears modest at best". No QA of RT stated. **C3**
Mucositis area % **confluent, %** **Dysphagia gr 3–5 %** **Weight loss % kg** A 40 27 24 5.1 B 30 14 17 3.3 p=0.03 p=0.002 p=0.006 p=0.009 No sign difference in frequency of thick pseudomembranes. No sign diff in pain at swallowing.	Sign imbalance in tumour sites between groups. The study suggests that the bacterial and fungeal flora is involved in the mucositis process and manipulation of the oral flora may have beneficial effects. The most relevant is probably the effect on dysphagia. As there was no relief of pain on swallowing it is difficult to interpret to what extent the pts experienced a true benefit. **C2**
Regarding the outcome of pts' assessment see [5]. In this paper the baseline assessments of the questionnaire are given and the difference in scoring at 11 months is 0.62 "units" on a 10 grade Likert (nominal) scale.	It is dubious to perform calculations on values from a nominal scale. To perform t-test on such material is debateable. See ref. [5]. **C3**
Evaluated after 3 w RT **Mucositis (gr 3–5)%** **Pain (gr 3–5)%** A 32 32 B 21 ns 18 ns No sign differences were found for mucositis or pain duration.	Heterogeneous material. Mucosal volume assessed. Sign correlation between area of irradiated mucosa and max. grade mucositis. **C3**

Overview 4 *Head and neck cancer. Radiotherapy – hypoxic cell sensitizers.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
van den Bogaert 1995 [39]	See overview 2.	
Eschwège 1997 [14] C MC	OS, LRC with etanidazole **A:** RT 2.0 Gy/fr,66–74 Gy/6.5–7.5 w (2 w split allowed) **B:** Same RT + etanidazole	1987–1990 SCC, all sites. St any T, any N, M0 A 187 pts B 187 pts
Lee 1995 [22] C MC	OS with etanidazole **A:** RT 2.0 Gy/fr, 66–74 Gy/6.5–7.5 w **B:** Same RT + etanidazole	1988–1991 SCC, oral, oroph., nasoph., supraglottic larynx., hypoph. St III–IV, M0. Base of tongue, St II–IV, M0. A 252 pts B 252 pts
Overgaard 1998 [31] C Double blind MC	LRC with nimorazole **A:** 2.0 Gy/fr, 62–68 Gy/6–7 w + placebo **B:** Same RT + nimorazole	1986–1990 SCC, pharynx, st I–IV, M0. Supraglottic, st II–IV, M0. A 195 pts B 219 pts

d: day(s); RT: radiotherapy; f: fraction(s); LRC = locoregional control; m: month(s); MC: multi-centre; ns: not significant; pts: patient(s); OS: overall survival; QA: quality assurance; SC: single-centre; SCC: squamous cell carcinoma; sign: significance; y: year(s)
Ref [14] and [22]: Etanidazole 2 g/m^2, 3 d/w for 17 RT days
Ref [31]: Nimorazole 1.2 g/m^2 during the first 30 treatment days

Results	Conclusion/Comments
Follow-up median 5 y **OS% LRC, at 2 y** A 54 53 B 54 ns 53 ns No difference in acute and late RT related side effects.	Major deviations from RT protocol, 10%. **C2**
Follow-up median 3.4 (1–5.6) y **OS% LRC%, at 2 y** A 41 40 B 43 ns 40 ns No difference in acute or late RT related side effects. Subgroups analysis showed sign survival benefit for N0–1 pts in B.	Early results. **C2**
Follow-up minimum 112 (84–170) m **OS% LRC%, at 5 y** A 16 33 B 26 ns 49 p=0.002 (OR 1.97 95% CI 1.33–2.93) No sign difference in acute or late side effects	There is an imbalance in the pts material with over-representation of Stage IV in group A, 46% vs. 37% in group B (sign). **C2**

Overview 5 *Head and neck cancer. Radiotherapy – miscellaneous studies: 1) fast neutrons; –2) radiotherapy compared to surgery alone; –3) influence of treated volumes.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Maor 1995 [27] C MC	1) OS and LRC with fast neutrons **A:** RT (X-rays) 2.0 Gy/fr, 70 Gy/7 w or 2.2 Gy/fr, 66 Gy/6 w **B:** Fast neutrons 20.4 Gy/12 f/4 w	1986–1991 SCC, diff sites. Stage III–IV, M0. A 83 pts B 86 pts
Zhang 1998 [43] C SC	2) OS and RC after preoperative RT vs surgery alone **A:** Surgery alone **B:** Preop RT 2.0 Gy/fr, 40 Gy/4 w + surgery	1981–1994 SCC, supraglottic ca. St I–IV, M0 A 102 pts B 99 pts
Chatani 1996 [7] C SC	3) RT volume – side effects and LC **A:** RT 2.0 Gy/fr, 60 Gy/6 w to field 6 x 6 cm^2 A 128 pts **B:** Same RT to field 5 x 5 cm^2.	1982–1992 SCC, glottic cancer. St T1N0, M0 B 85 ns 85 ns B 132 pts

d: day(s); f: fraction(s); LC: local control; LRC: locoregional control; m: month(s); MC: multi-centre; ns: not significant; OS: overall survival; QA: quality assurance; RC: regional control; RFS: relapse free survival; RT: radiotherapy; SC: single-centre; SCC: squamous cell carcinoma; sign: significant; sr: stage; w: week(s); y: year(s)

Results	Conclusion/Comments
Follow-up median 3.5 (0.25–6.7) y **OS% LRC%, at 3 y** A 27 68 B 27 ns 63 ns No diff in acute side effects. Late side effects gr >3 sign more frequent in B p=0.008.	RT procedures and radiation qualities poorly stated. Small study. **C3**
Follow-up 3 y **OS%, at 5 years** A 73 B 69 ns RC not sign different between group A and B.	RT dose lower than usually given. Subgroup analysis showed sign higher RC in st I-III pts in group B (A 75%; B: 90%, p=0.02). Relapse rate in contralateral neck sign higher in group A (p=0.02). **C3**
Follow-up median 6 (2–12) y **OS% RFS%** A 87 87 Late effects with laryngeal oedema and benign polypoid lesion more frequent in A (A: 31 pts; B: 19 pts, p=0.03)	No QA of RT stated. Smaller volume seems to result in less late side effects. **C2**