5. **Non small Cell Lung Cancer**

Introduction

The cancer registry in Sweden shows a continuous increase of lung cancer cases from 867 in 1958 when the registry started to 2 846 in 2000. The Swedish cancer registry also shows that the incidence of lung cancer in males has decreased between 1991 and 2000 (from 47/100 000 to 40.8/100 000) whereas it increased in females during the same period (from 20.7/100 000 to 25.5/100 000). With a 5-year survival in the range 10–14 per cent, lung cancer is the leading cause of cancer death in the industrialized world and accounts for about one million deaths worldwide every year [105]. Tobacco smoking is the main etiology causing approximately 90 per cent of cases [61]. Passive smokers are also at increased risk of lung cancer [98]. Radon exposure and certain occupational agents such as arsenic, asbestos, chromium, nickel and vinyl chloride increase the risk for lung cancer. Smoking has an additive or multiplicative effect with some of these agents [105].

Non-small cell lung cancer (NSCLC), includes the histological types adenocarcinoma, squamous cell carcinoma, large cell undifferentiated carcinoma, adenosquamous carcinoma and accounts for 80–85 per cent of all lung cancer cases, the remaining 15–20 per cent being small cell lung cancer (SCLC). NSCLC and SCLC are two different therapeutic entities [41]. SCLC, at least initially, is characterized by relative high sensitivity to cytotoxic drugs and radiotherapy while NSCLC often presents as being chemo- and radioresistant [51]. The present report does not include SCLC.

The TNM classification for lung cancer was revised in 1997 [72], (Table 1). Untreated NSCLC has a dim prognosis even in early stages. In a retrospective analysis of 130 patients not receiving any anticancer treatment no stage IB patients were alive at 3 years [108].

Table 1 *TNM classification for lungcancer.*

Stage	TNM subset
0	Carcinoma in situ
IA	T1N0MO
IB	T2N0M0
IIA	T1N1M0
IIB	T2N1M0, T3N0M0
IIIA	T3N1M0, T1–T3N2M0
IIIB	T4N0–N3M0, T1–T3N3M0
IV	any T any N M1

TX Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 No evidence of tumour
Tis Carcinoma in situ
T1 Tumour <3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus
T2 Tumour with any of the following features of size or extent: >3cm, involves main bronchus >2 cm distal to carina, invades the visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3 Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus <2 cm distal to carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4 Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumour with a malignant pleural or pericardial effusion, or with satellite tumour nodule(s) within the ipsilateral primary tumour lobe of the lung
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumour
N2 Metastases to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastases to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
MX Presence of distant metastases cannot be assessed
M0 No distant metastases
M1 Distant metastases present

Summary of the earlier report, SBU 129/2

Conclusions

- Surgery constitutes primary treatment for non-small cell lung cancer (NSCLC) stages I and II. Radiotherapy may provide an alternative for patients who are inoperable for medical reasons.
- The value of radiotherapy following radical surgery for NSCLC remains to be shown. It is not indicated based on current knowledge.

- For NSCLC stage III, radiotherapy shrinks tumours and prolongs survival at two and three years. Whether it influences long-term survival after five years has not been shown. Considering the side effects of treatment, one must question whether limited improvements in survival motivate routine radiotherapy in these patients.
- Earlier attempts to add chemotherapy to radiotherapy to improve treatment results of NSCLC have not yielded convincing results. Several studies are currently on-going.
- Prophylactic cranial irradiation (PCI) is not indicated in patients with NSCLC.
- Radiotherapy is an important treatment alternative in special palliative situations involving severe cough, severe bleeding, pain, pulmonary obstructions, and vena cava superior syndrome. In these situations, good results may be achieved with few fractions.

Discussion

The SBU 129/2 report on NSCLC reviewed the experience using definitive RT in medically inoperable patients with stage I and II NSCLC, post-operative RT in radically resected patients with NSCLC, definitive RT for stage III NSCLC alone or combined with chemotherapy and palliative RT. The report covered the literature until 1992 and it was published in 1996. The recommendations of SBU 129/2 concerning medically inoperable patients with stage I and II are congruent with results published in the literature after 1992. More data and an important meta-analysis [5] on postoperative RT were published after 1992. These data strengthen the recommendation against the use of postoperative RT in early stages NSCLC.

The recommendations of SBU 129/2 concerning the use of RT for stage III NSCLC are now outdated. The meta-analysis on chemotherapy in NSCLC published in 1995 [3] and several randomized studies in locally advanced disease published between 1992 and 1996 were not included in the SBU 129/2 but have had a great influence on the standard of care for stage III NSCLC during the last five years. In 1997 the ASCO

(American Society of Clinical Oncology) clinical practice guidelines for unresectable NSCLC [4] recommended (grade A) that chemotherapy in association with definitive RT is appropriate for selected patients (performance status 0,1 and possibly 2) with locally advanced disease (level of evidence I). The SBU 155/2 report on chemotherapy for cancer published February 2001 stated that induction cisplatin-based chemotherapy before radical RT modestly prolongs long-term survival and that concomitant chemotherapy and RT with cisplatin or carboplatin may enhance local control and long-term survival.

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	1/2 103	1/1 911	–	**2/4 014**
C	4/1 204	17/4 137	8/1 606	**29/6 947**
P	3/256	12/555	4/333	**19/1 144**
R	4/9 875	12/5 022	5/1 170	**21/16 067**
L	3	2	–	**5**
O	–	3	1	**4**
Total	**15/13 438**	**47/11 625**	**18/3 109**	**80/28 172**

*) In the table are included studies concerning small-cell lungcancer as well as non-small cell lungcancer.

Assessment of new literature

Search methods and selection

The literature search was performed according to the directions decided by SBU. The reports were identified by searching Pubmed, Medline, and the Cochrane Library. The time period chosen was from January 1, 1992 to May 1 2001. One study published before 1992 was also included as it was updated 1996 and it is important to discuss it in the context of combined chemo-radiotherapy in locally advanced NSCLC. Several studies published before 1992 and important reviews are commented on but not included in the tables. The search criteria used were: full report in a peer-reviewed scientific journal, dealing with randomized controlled trials, meta-analysis, prospective phase I and II studies and retrospective

studies. Totally 266 reports were initially retrieved. Only 65 reports were included in this analysis.

As well conducted randomized trials have been performed for the most important issues concerning RT in NSCLC, this report is mainly based on these studies. The major exceptions are the analysis of RT for medically inoperable patients with NSCLC, stage I/II, mainly based on retrospective reports and analysis of trimodality treatment including RT, chemotherapy and surgery mainly based on phase II data. Most of the published phase I/II trials dealing with neoadjuvant chemotherapy followed by RT or concomitant chemo-radiotherapy were excluded from this report. The report focuses almost exclusively on external beam RT. Endobronchial brachytherapy is reviewed in the context of palliative treatment.

Treatments of NSCLC with other radiation qualities such as neutrons, protons and light ions are not reviewed in this report.

The reasons for exclusion of 201 reports were:
- studies based on small patient material
- experimental phase I/II studies

Overview of new studies

Radiotherapy for medically inoperable patients or patients refusing surgery with NSCLC stage I and II

Overview 1 (after the list of references)

Surgery is the treatment of choice for stage I and II NSCLC but for medically inoperable or patients refusing surgery radiotherapy (RT) has been offered as treatment alternative [90]. No randomized trials of RT versus no intervention have been conducted during the last 30 years. Since 1992 twelve studies, including 1 247 patients, focusing on RT for early stage NSCLC, have been published, the majority being retrospective analysis. The majority of these patients were stage I. In the non-randomized studies conventional radiation schedules were mostly used but hyperfractionated non-accelerated [48] and hypofractionated [93,95] schedules were also studied. Five studies included between 100 and 150 patients/study [15,39,54,70,91] and the largest series (347 stage I patients) was reported by Gauden *et al* [36]. In several studies the total dose

and/or fraction dose were heterogenous [42,50,56,91]. However, there were no large dose variations between these studies, the average total dose being 60 Gy. Doses >65 Gy were associated with increased local control compared with doses <65 Gy [50,56].

In addition, the large randomized CHART (Continous hyperfractionated accelerated radiotherapy) study focusing on altered fractionation of RT included 203 (of totally 563) patients stage I and II [81]. The increased efficacy of CHART compared to conventional fractionation in terms of local control and survival was preserved in the subset of patients with stage I and II disease [81]. However, the survival benefit associated with CHART was confined to patients with squamous cell carcinoma.

Treatment volumes varied considerably between different studies, from small fields encompassing only gross tumour to large fields aimed at prophylactic lymph node coverage. There was no proven advantage for node irradiation in these patients [48,90]. Several studies showed that small tumours (<3 cm) were better controlled with RT compared with larger tumours and a correlation between tumour size, local control and survival was found [36,54,56,70,95].

Serious side effects were uncommon after doses of 60–66 Gy in this population of frail patients. Dose escalation to limited fields using 3-D planning, aimed to improve local control, has been attempted and dose escalation beyond 100 Gy has been achieved in small target volumes [43].

The main issue for RT for stage I/II NSCLC is whether this modality is associated with a reasonable cure rate for these patients and thus can be offered as a therapy with curative intent. Average survival data from these studies showed that approximately 15–20 per cent of patients (range 6–30 per cent) were long term survivors, 25 per cent died of intercurrent disease, 20–30 per cent died of distant metastatic disease and 30 per cent died of local failure only. Thus, the majority of these medically unfit patients died of uncontrolled lung cancer and not of intercurrent disease. Local failure was a major problem and strategies aimed to optimize RT in order to improve local control may also improve survival.

The literature shows that:

- RT for medically inoperable patients or patients refusing surgery with NSCLC stage I and II is an alternative treatment with curative potential.
- Doses exceeding 65 Gy are associated with increased local control.
- Continous hyperfractionated accelerated RT showed in one randomized trial a survival benefit compared with conventional RT in patients with squamous cell lung cancer.

Postoperative radiotherapy in radically resected NSCLC

Overview 2 (after the list of references)

Postoperative RT has been widely administered to patients, radically operated for NSCLC, for almost four decades and was aimed to decrease local recurrence and increase survival [5]. However, no randomized trial before [5] or after 1996 [26,34,67] has shown a survival benefit with this approach.

The PORT (postoperative radiotherapy) meta-analysis [5] includes only trials randomizing to RT or no further treatment after radical surgery between 1980–1996 (six trials published, three unpublished). Some trials included only pN0 disease [57], others only pN1/N2 [96] or pN2 disease [27] but the majority included a mixture of resectable TN categories. This meta-analysis shows a significant adverse effect of postoperative RT on survival with an absolut detriment of 7 per cent at two years. A subgroup analysis showed that the detrimental effect was confined to stage I/II (N0, N1 disease). For N2 disease there was neither significant adverse effect nor evidence of benefit. The results of the PORT meta-analysis were confirmed by a large randomized trial [26].

Decreased rates of recurrence at the bronchial stump and mediastinum with postoperative RT were reported by Austrian investigators [67]. However, increased local control did not translate in increased survival. Also in a study, reported by Chinese investigators [34], postoperative RT significantly reduced local relapses, but did not improve overall survival probably due to a high frequency of distant metastases in this patient group.

The literature shows that:

- Postoperative RT has a detrimental effect on survival for patients with radically resected stage I and II NCLC.
- The role of RT for radically resected stage III NSCLC is not established and requires further investigation.

Radiotherapy for locally advanced NSCLC, (stage IIIA/N2 and IIIB)

At diagnosis, 35–40 per cent of all NSCLC cases are locally advanced and regarded primarily unresectable [25]. RT as a single treatment modality has been the standard for unresectable stage III NSCLC in the eighties [103]. The results of RTOG (Radiation Therapy Oncology Group) 7301 trial, reported 1987, [74] randomizing 551 patients to 40 Gy continuously or 40 Gy split course or 50 Gy continuously or 60 Gy continuously (all four arms with 2 Gy per fraction daily, five days per week) established a total dose of 60 Gy continuously as standard RT regime for NSCLC on the basis of superior results at the 3-year follow-up for the 60 Gy arm (36 per cent local failure compared with 63 per cent for the 40 Gy arms). However, at five years tumour control (local failure 70 per cent) and survival (7 per cent) was identical in the 60 and 40 Gy arms. "Curative" RT (60 Gy with 2 Gy per fraction) is associated with a 5-year survival of 5–7 per cent and results from a phase III study, including 319 patients, questions if this treatment prolongs survival for patients with locally advanced NSCLC [49]. In this trial, patients were assigned to receive either RT (60 Gy with 2 Gy per fraction) or vindesine 3mg/m^2 weekly or RT and vindesine. Albeit response rates were superior in the RT arms no significant differences concerning median and long term survival were observed.

Altered fractionation schedule with or without chemotherapy in patients, medically inoperable or with locally advanced, unresectable, NSCLC

Overview 3 (after the list of references)

Split course RT had been widely used in the 60s and 70s albeit no randomized study in that period showed superiority for this regimen compared with continuous RT [68]. Data from Perez et al [74] showed better local control with continuous compared with split course RT. A more

recent randomized trial comparing split course with continuous RT showed no benefit for the split course regimen [80].

A retrospective analysis of data from RTOG 9311, RTOG 8321 and RTOG 8403 focused on the effects of prolongation of RT by "unplanned splits" [21] and found that in patients with favourable prognostic factors (good performance status, minimal weight loss) interruptions, delaying the completion of RT, negatively affected long-term survival.

The poor rates of local control achieved with "standard" RT (60 Gy in 6 weeks, 2 Gy/fraction) [74] and the radiobiological considerations of circumventing repopulation between fractions and minimize long-term normal tissue toxicity [82] were the starting points for investigation of new fractionation schemes. Hyperfractionated radiotherapy, HRT, (without acceleration), allows delivery of a higher total dose without increase of late toxicity [102]. In the RTOG 8311 phase I/II trial, published 1990, escalation of HRT (1.2 Gy twice daily) was achieved up to 79.2 Gy [20]. In a subset analysis of patients with good performance status, the dose of 69.6 Gy was associated with higher median and 2-years survival compared with lower doses. However when tested in a randomized setting in the RTOG 8808/ECOG (Eastern Cooperative Oncology Group) 4588 trial [85,86] hyperfractionated non-accelerated RT showed no advantage in terms of long-term survival compared with the standard RT arm.

Hyperfractionated accelerated radiotherapy with acceleration, HART, allows an overall decrease in total treatment time without increasing long-term normal tissue toxicity [82]. Theoretically, decrease in total treatment time should minimize tumour cell repopulation thus increasing the efficacy of RT. After encouraging preliminary results [83], continuous hyperfractionated accelerated radiation therapy (CHART) has been tested in a large randomized trial [81]. The median and 2-year survival favored CHART and the difference was still significant at three years suggesting a long-term survival advantage for CHART. However, this advantage was confined to tumours with squamous histology. For non squamous histologies (adenocarcinoma, large cell undifferentiated carcinoma) there was a trend favouring the conventional RT albeit not reaching statistical significance. Esophageal but not pulmonary toxicity was more common with CHART compared with conventional RT.

Conventional and accelerated RT, albeit not the CHART schedule, were compared in two small randomized trials, [10,13], both of them underpowered. No advantage for these accelerated schedules were detected.

Further development of the CHART regime has been slowed by the personnel and logistic problems associated with three treatments per day including weekends. To overcome some of these logistic problems accelerated RT regimens without treatment on weekends, (HART or CHARTWEL) have been developed in Europe [84] and USA [53,69].

The CHARTWEL regime, given over 16–18 days has been employed to investigate dose escalation in the context of accelerated RT [84]. HART regimens, using 2 [53] or 3 fractions/day [69] has, in phase II setting, produced results similar to those obtained with CHART (1-year survival 57–61 per cent) but no randomized trial comparing HART with CHART or conventional RT has been performed.

Hypofractionation has been widely used in the context of palliative RT [1,2] but not for RT with curative intent due to concern for increased risk of long-term complication. However, hypofractionated schedules were used by Dutch investigators for treatment of medically inoperable early stage NSCLC with results comparable with conventional RT [93,95]. The same investigators designed hypofractionated RT schedules for unresectable, stage III, NSCLC. The results of a large phase II study using three different schedules show very low overall survival [94]. In only one subgroup were the results comparable to those obtained with conventional RT.

The literature shows that:

- Split course RT has been of no advantage compared to continuous RT schedules. Prolongation of the treatment time by planned splits or unplanned delays may negatively influence local control and long term survival.
- Hyperfractionated not accelerated RT (HRT) has not shown any survival advantage compared with conventional RT.
- Continuous hyperfractionated accelerated RT (CHART) has greater efficacy compared with conventional RT in locally advanced NSCLC. The benefit is limited to squamous cell histology.

Target definition and RT planning

The standards of late 1980s and early 1990s for dose, volume and beam arrangements for RT of NSCLC were established by the RTOG 7301 trial [74]. In this study RT to a total dose of 60 Gy delivered with 2 Gy per fraction daily during six weeks was superior in terms of local control compared with schedules containing splits or lower total dose. Large volumes of lung, hilar and mediastinal nodes were included in the treatment volume. Prophylactic irradiation included not only hilar and mediastinal node stations but even supraclavicular nodes. The poor local control and 5-year survival in patients receiving this standard RT [49,74] and the theoretical radiobiological considerations [104] that doses up to 100 Gy may be necessary to control tumours >5 cm show that both dose and treatment volume are crucial points for the success of RT. The dose escalation attempted in the RTOG 8301 trial by using hyperfractionation without acceleration was not accompanied by reduction of treatment volume and the survival benefit seen at 69.6 Gy was obliterated at higher doses by a high rate of pneumonitis [20].

The controversy of "locoregional" RT covering node stations at risk for micrometastatic involvement versus "local" RT covering gross intrathoracic disease is still a controversial topic. Albeit no comparative trial of RT with versus without elective nodal irradiation has shown increased efficacy for RT with prophylactic node covering, several authors advocate this approach by pointing out the limited evidence for the benefit of dose escalation beyond 60 Gy and the reality of micrometastatic disease in mediastinum [59]. However, the prevailing opinion, especially in the context of RT combined with chemotherapy is that RT is a local therapy and elective node irradiation should be omitted to allow reduction of treatment volumes and dose escalation using 3-D (threedimensional) planning [106]. Results in NSCLC stage I/II where elective nodal irradiation has been omitted without compromising local control and survival and the low rate of controlling the gross intrathoracic disease using the "old standard" of 60 Gy support the argument "why worry about disease you cannot see when you cannot control the disease that you can see" [104]. It must also be remembered that the "old standard" of large fields was settled at a time where the 3-D tools were unavailable and the staging tools more crude compared to the modern techniques and that the

biological model for the large fields was Hodgkin's lymphoma and not NSCLC [106]. Cisplatin-based chemotherapy has shown the potential to control subclinical disease [22] although it is still unclear whether there is a substantial control of subclinical disease in the mediastinum.

Modern 3-D planning includes target definition using 3-D volume techniques, virtual simulation, 3-D dose calculation and dose-volume histogram plan evaluation. Computer-simulated studies comparing 3-D with 2-D (twodimensional) techniques have demonstrated the possibility of dose escalation and reduction of dose to normal tissue [9,38]. These results have been tested in the clinic. The 3-D planning has allowed dose escalation beyond 60 Gy, reduction of pulmonary toxicity and 2-year survival of 33–37 per cent which compare favourably to results achieved by RT to 60 Gy using large fields [8,44,92].

The rapid development of PET (positron-emission tomography) offers a promising tool for better target definition. PET scans have better sensitivity and specificity than CT scans [65]. A meta-analysis including 2 740 patients in 43 studies showed that PET is significantly more accurate in detecting nodal disease [30].

The literature shows that:

- There is no evidence that thoracic RT using large fields for elective covering of mediastinal lymph nodes is superior in terms of local control and survival in patients with NSCLC compared to RT given only to the gross tumour volume. As large volumes are associated with increased toxicity, most authors favour RT given to the gross tumour volume and emphasize the quality of treatment planning, 3-D protocols being increasingly used.

Neoadjuvant chemotherapy plus radiotherapy versus radiotherapy alone or chemotherapy alone

Overview 4 (after the list of references)

Analysis of patterns of relapse in different studies using RT for locally advanced NSCLC provided clues for development of new strategies. In RTOG 7301 [74] 40–65 per cent of patients had an extrathoracic first relapse site, indicating that systemic therapy with cytotoxic drugs

may be added to RT to improve treatment outcome. After several phase II trials indicating superior results with neoadjuvant chemotherapy followed by RT [11,31] several randomized trials comparing this modality with RT alone were conducted in both USA and Europe in late eighties and early nineties. These studies yielded both negative [66,71,101] and positive [24,29,58,86] results. A study reported by Swedish investigators showed a positive trend for the combined modality arm albeit not reaching statistical significance [14].

Noteworthy the negative trials employed either chemotherapeutic combinations with alkylating agents [71,101] or low dose cisplatin [66] whereas the positive trials employed cisplatin-based chemotherapy with a cisplatin dose of 100 mg/m^2/3w [29,58,86] and 50 mg/m^2/3w [24].

The first positive trial reported was CALGB (Cancer and Leukemia Group B) 8433 and it had a great impact on clinical practice for locally advanced NSCLC [29]. Mature results from this study showed a significant survival benefit in the combined treatment groups which is maintained at the 7-year follow-up.

In a large French trial the patients had Karnofsky performance status better than 50 per cent and adenocarcinoma histology was excluded [58]. This trial is of particular interest because the local control was assessed carefully by both radiological and endoscopical studies. Local control at one year was poor in both arms. The survival advantage in the combined modality group was due to lower distant metastases rate compared with the RT group.

Mature results [85] from the RTOG 8808/ECOG 4588 study first reported 1995 [86] still show advantage for the combined modality group, however the difference is not so large as in CALGB 8433 [28].

Other smaller randomized trials (<100 patients included) comparing neoadjuvant chemotherapy followed by RT versus RT alone published after 1992 were either negative [40], positive [107] or did not reach statistical significance but showed a positive trend for the combined modality group [23]. Interestingly, in the trial reported by Wolf et al [107] concomitant low dose weekly cisplatin was used in both arms as a radiosensitizer and the neoadjuvant regimen was a non-platinum combination.

The impact of RT in patients with locally advanced NSCLC treated with cisplatin-based chemotherapy was investigated by Japanese investigators [55]. Albeit a small trial, it showed significantly improved survival in the RT containing arm compared with chemotherapy alone. A European trial [89] randomized responders after three cycles of cisplatin-based chemotherapy to either RT or further chemotherapy. Albeit better local control was observed in the RT group there was no significant survival difference between the two groups. However, only the patients responding to chemotherapy were included in this trial and the results cannot be extrapolated to a chemonaive population.

The trials of neoadjuvant cisplatin-based chemotherapy and RT versus RT alone were conducted in the mid 1980s and early 1990s. The radiotherapy delivered was 60–65 Gy to the gross intrathoracic disease and 40–50 Gy as elective prophylactic irradiation of mediastinal nodes. The RT planning was of low quality seen from the perspective of year 2002 standards. The uncertainty of target delineation and localization was a major problem when RT delivery was analysed. In the CALGB 8433 [28] trial, a retrospective quality control review identified that in 23 per cent of the radiation treatments, the portal films failed to completely encompass the tumour [29].

Another problem with these trials is the lack of information concerning quality of life, an increasingly important issue especially in the context of aggressive multimodality treatments.

The literature shows that:

- In four well conducted randomized trials cisplatin-based neoadjuvant chemotherapy followed by thoracic radiotherapy provided a modest but significant survival advantage compared with radiotherapy alone in patients with good performance status. The survival advantage was associated with decreased rate of distant relapse but not with increased local control in patients treated with chemotherapy and radiotherapy compared with radiotherapy alone.

Radiotherapy with concomitant chemotherapy [10,12,13] neoadjuvant chemotherapy and radiotherapy versus neoadjuvant chemotherapy and radiotherapy with concomitant chemotherapy [19], radiotherapy with neoadjuvant chemotherapy versus radiotherapy with concomitant chemotherapy

Overview 5 (after the list of references)

Another approach to improve the therapeutic effect of RT is based on preclinical studies with cytotoxic drugs showing potential to act as radiosensitizers. The recognition of cisplatin as radiosensitizer laid the rationale for studies using low dose cisplatin concomitant with RT. The study reported by Trovo et al showed no benefit for this approach compared with RT alone [100]. The larger EORTC (European Organization for the Research and Treatment of Cancer) trial investigating both the daily and weekly schedule of cisplatin showed improved survival with daily low dose cisplatin [88]. The distant metastases rate was not affected by addition of cisplatin to RT. When cisplatin was administered every 3rd week concomitantly with RT no survival advantage was detected compared with RT alone in a trial including 240 patients [12].

The two consecutive trials reported by Jeremic et al [46,47] used carboplatin and etoposide as radiosensitizing chemotherapy and hyperfractionated but not accelerated RT. Mature results are available from both trials and show long term benefit for combined modality. In an underpowered four armed randomized trial the addition of carboplatin to either conventional or accelerated RT did not improve survival compared with RT alone [10].

Drugs of the 3rd generation as paclitaxel, docetaxel and gemcitabine have shown impressive radiosensitizing properties in vitro [60]. Phase II trials using weekly paclitaxel [18], weekly paclitaxel and carboplatin [17] or docetaxel [52] show impressive local control rates and have become very popular in clinical practice. However, no randomized trials exploring the superiority of these regimens compared with combined modality treatment using older cisplatin-based chemotherapy have been conducted. Moreover, concern has been raised about unexpected toxicities associated with concomitant chemo-radiotherapy and 3rd generation drugs. In a small

non randomized trial concomitant paclitaxel and RT has been associated with a relatively high risk of opportunistic lung infections [76].

The CALGB 9130 trial [19] used both neoadjuvant and concomitant chemotherapy to improve the effect of RT. The median survival and 2-year survival did not differ between the groups. Mature results at four years showed no benefit for the addition of carboplatin concomitantly with RT.

The use of drugs with no significant activity against NSCLC but having radiation-enhancing properties has also been studied in patients with locally advanced disease. Lonidamine is such an agent and has been studied as radiation-enhancer in a randomized trial. Addition of lonidamine to RT showed no benefit compared with RT alone [87].

As in the case of the randomized trials focused on neoadjuvant chemotherapy followed by RT, the trials of concomitant chemo-radiotherapy did not systematically address the question of quality of life.

The literature shows that:

- Cis- or carboplatin-based chemotherapy concomitant with radiotherapy showed increased efficacy for local control compared with radiotherapy alone. However, the optimal chemotherapy schedule in this setting is not defined. The survival benefit was associated with increased local control and not with decreased risk for distant metastases.

Neoadjuvant versus concomitant chemo-radiotherapy

To this date only two phase III trials addressed this question. In the first trial [35] (overview 5) median survival at 2 and 5-years in the concomitant group was significantly superior compared with the neoadjuvant group. Myelosuppression was more common in the concomitant group whereas esophageal toxicity was identical in the two groups.

The second trial RTOG 9140, not yet published, randomized 611 patients to (A) two cycles of cisplatin + vinblastine followed by RT 60 Gy (1.8 Gy qd) or (B) the same chemotherapy concomitantly with the same RT or (C) cisplatin+etoposide concomitantly with hyperfractionated non accelerated RT (69.6 Gy, 1.2 Gy bid). Preliminary results were presented

at the ASCO (American Society of Clinical Oncology) meeting 2000 (ASCO, 2000, 19, 1891). The median survival was significantly higher in arm B compared with arm A (17 versus 14.6 months). Acute esophageal toxicity was higher in arm B compared to arm A. However, the results in the second concomitant arm (C) were not superior to arm A.

These two trials support the concept of concomitant chemo-RT in locally advanced NSCLC in terms of efficacy. However, this approach is associated with increased toxicity. Noteworthy, the design of these trials using full dose chemotherapy was different from the design of the EORTC [88] and Yugoslavian trials [46,47] (overview 5) where chemotherapy was administered with low dose and dose dense schedules.

The literature shows that:

- Concomitant cisplatin-based chemotherapy and radiotherapy showed, in two randomized trials, increased efficacy but also increased toxicity compared with neoadjuvant cisplatin-based chemotherapy and radiotherapy. The second trial (ASCO, 2000) is not published and mature results are warranted.

meta-analysis of combined chemo-radiotherapy versus radiotherapy alone

Three large meta-analysis aimed to establish the value of chemotherapy combined with RT in locally advanced NSCLC were published 1995 and 1996 [3,64,75], (Overview 4).

The results of these three meta-analysis show a modest but significant benefit for cisplatin based combined chemo-RT compared with RT alone. One of the meta-analysis used a rigorous methodology based on updated individual patient data and had a great impact in establishing the combined modality chemo-RT as standard of care for patients with locally advanced NSCLC and good performance status [3].

The literature shows that:

- Cisplatin-based chemotherapy in either neoadjuvant or concomitant combination with RT provides a modest but significant survival rate advantage compared with RT alone.

Chemo- radiotherapy before surgery in NSCLC (trimodality treatment)

Overview 6 (after the list of references)

RT as induction therapy before surgery was studied from the 1950s to early 1970s but no survival benefit has been shown [73]. Many investigators focused on chemotherapy as induction before surgery and two small randomized trials reported improved survival with this bimodality treatment compared with surgery alone [78,79].

Using the experience of neoadjuvant chemotherapy and combined chemo-radiotherapy, trimodality treatment including RT, chemotherapy and surgery have been increasingly used in patients with tumour considered unresectable at diagnosis [32]. Still only phase II trials are reported.

The largest trials focused on trimodality for locally advanced unresectable NSCLC were performed by SWOG (Southwest Oncolgy Group) [7] and by German investigators [33]. Both trials recruited patients with locally advanced disease. RT was given either conventionally [7] or as HART [33]. Chemotherapy consisted in both trials of cisplatin and etoposide given either concomitantly with RT [7] or as neoadjuvantly and concomitantly with RT [33]. Two other smaller phase II trials have investigated trimodality treatment [16,99]. The high predictive value of pathologic complete remission and/or sterilisation of mediastinal lymph nodes and the rates of these remissions, being comparable with the long-term survival rates, question the therapeutic role of surgery in this setting. Randomized trials focused on this issue are now performed.

The literature shows that:

- Patients with locally advanced NSCLC, unresectable at diagnosis, treated with combined cisplatin-based chemo-radiotherapy may be completely resected in 50–80 per cent of cases and achieve 20–35 per cent long-term survival. However, it has not been determined whether the role of surgery in this setting is therapeutic or prognostic. Several ongoing randomized trials address this issue.

Palliative radiotherapy for control of symptoms related to intrathoracic tumour

Overview 7 (after the list of references)

Randomized trials of chemo-radiotherapy and one meta-analysis [3] showed that the benefit of combined modality therapy is limited to patients with good prognostic factors (good performance status, minimal weight loss). For many patients, with locally advanced disease and poor performance status, less aggressive treatment approaches are required to palliate symptoms associated with the intrathoracic tumour burden: cough, haemoptysis, dyspnea due to central airways obstruction, chest pain, dysphagia, vena cava superior syndrome. Also many patients with distant metastatic disease need palliation of symptoms caused by the intrathoracic component of their disease. Radiotherapy is an acceptable method to relieve these symptoms [4].

The British Medical Research Council (MRC) conducted two randomized trials focused on fractionation of palliative thoracic RT. The first trial showed that 2 fractions of 8.5 Gy spaced by one week (totally 17 Gy) gives as effective palliation as 30 Gy given in 10 fractions [1]. The second trial compared 17 Gy given in 2 fractions with a single 10 Gy fraction [2]. The single 10 Gy fraction has the same palliative efficacy as the 2 fraction regimen. MRC pursued the investigation of an optimal palliative RT schedule and conducted a large randomized trial comparing 17 Gy in 2 fractions with a more intensive RT consisting of 39 Gy in 13 fractions [62]. Survival, palliation of symptoms and quality of life were the main endpoints. The 2 fraction regimen had a more rapid palliative effect whilst the more intensive 13 fractions regimen was associated with a longer survival. Another trial compared 17 Gy in 2 fractions to 22.5 Gy in 5 fractions [77] and showed equivalent palliative efficacy of two schedules. Haemoptysis and chest pain but not other symptoms were palliated for eight weeks.

A number of patients with advanced disease may have thoracic symptoms which are mainly related to the endobronchial component of their tumour. Such symptoms are cough, haemoptysis, breathlessness and obstructive pneumonia. Endobronchial brachytherapy has been widely

used to palliate such symptoms [45]. There are many reports in the literature, the majority being small non-prospective studies. Results from large, single-institution series have also been reported. [37,63].

British investigators compared endobronchial brachytherapy with external beam RT as palliative treatment [97]. The endpoints of this study were symptom relief, quality of life and acute/late toxicity of the treatments. The authors concluded that conventional RT was preferable to endobronchial brachytherapy because it provided better overall and more durable palliation.

The literature shows that:

- Single large fraction or two large fractions of thoracic radiotherapy can be used to palliate symptoms caused by the thoracic tumour burden.
- A more intensive RT schedule (39 Gy in 13 fraction) is associated with increased survival compared to two large fractions but also with a delayed palliative effect.
- One randomized trial showed that external beam radiotherapy provided better and longer palliation compared with endobronchial brachytherapy. The role of brachytherapy in this context should be studied in prospective trials.

Literature

This report is based on four meta-analysis, 31 phase III randomized trials, 12 phase I and II non randomized trials and 12 retrospective studies including 18 310 patients. A total of 8 043 patients were included in randomized trials and the meta-analysis included 9 637 patients. There is a partial overlap concerning the total study population between the meta-analysis and some randomized trials (three meta-analysis of chemotherapy plus RT versus RT alone and randomized trials of neoadjuvant/concomitant chemotherapy + RT versus RT alone and the meta-analysis of postoperative RT and randomized trials of postoperative RT versus observation).

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	3/7 750	1/1 887	–	**4/9 637**
C	19/6 222	6/938	6/883	**31/4 550**
P	8/820	4/150	–	**12/970**
R	9/2 923	3/230	–	**12/3 153**
L	6	–	–	**6**
Total	**45/14 785**	**14/2 834**	**6/691**	**65/18 310**

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

There is a partial overlap between two meta-analysis and randomized trials of induction/concomitant chemotherapy + RT versus RT alone and meta-analysis of postoperative RT and randomized trials of post-operative RT versus observation.

Conclusions and Comments

Based upon the literature review, the following main conclusions can be drawn:

- A large clinical experience suggests that radiotherapy to medically inoperable patients or patients refusing surgery with NSCLC stage I/II prolongs survival, 15–20 per cent of these patients reaching long-term (5-year) survival (references listed in Overview 1). However, no randomized trials have adressed this issue.
- There is strong evidence that postoperative radiotherapy in radically resected stage I/II NSCLC does not prolong survival compared with observation alone. (C1[26], C1[34], M2[6], C1[96]).
- There is some evidence that continuous hyperfractionated accelerated radiotherapy (CHART) is associated with increased survival compared to conventional radiotherapy in locally advanced NSCLC and also medically unfit patients with stage I/II NSCLC. The benefit is however limited to squamous cell histology. (C1[81]).

- There is strong evidence that combined modality treatment with platinum-based chemotherapy and radiotherapy, either neoadjuvant or concomitant, is superior to radiotherapy alone in terms of survival in locally advanced unresectable NSCLC and should be the standard of care in patients with good performance status. (WHO 0,1) (C1[28], C1[58], M2[64], M1[3], M1[75], C1[85,86], C1[46], C1[47], C1[88]).
- There is some evidence that concomitant chemo-radiotherapy is associated with increased survival compared with sequential chemo-radiotherapy, albeit at the price of increased toxicity. (C1[35]).

Comment: Combined chemo-radiotherapy of primary non-resectable stage III NSCLC followed by surgery in responders lacks evidence from prospective randomized trials and cannot be recommended for routine use.

- There is strong evidence that radiotherapy can palliate of symptoms associated with the intrathoracic tumour burden. (C1[62], C1[2], C1[77]).
- There is some evidence that two large fractions may be as effective as conventional schedules consisting of 10–13 smaller fractions in terms of pallation of symptoms. (C1[62]).
- There is some evidence that endobronchial brachytherapy for palliation of symtoms associated with endobronchial tumours is not superior to external beam radiotherapy. (C1[97]).

References

1. Inoperable non-small-cell lung cancer (NSCLC): a Medical Research Council randomized trial of palliative radiotherapy with two fractions or ten fractions. Report to the Medical Research Council by its Lung Cancer Working Party. Br J Cancer. 1991;63:265-70.

2. A Medical Research Council (MRC) randomized trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Medical Research Council Lung Cancer Working Party. Br J Cancer. 1992;65:934-41. (C1)

3. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Non-small Cell Lung Cancer Collaborative Group. Bmj. 1995;311: 899-909. (M1)

4. Clinical practice guidelines for the treatment of unresectable non- small-cell lung cancer. Adopted on May 16, 1997 by the American Society of Clinical Oncology. J Clin Oncol. 1997;15:2996-3018.

5. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomized controlled trials. PORT Meta-analysis Trialists Group. Lancet. 1998;352:257-63. (M2)

6. Postoperative radiotherapy for non-small cell lung cancer. PORT Meta- analysis Trialists Group. Cochrane Database Syst Rev. 2000;2.

7. Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT, 3rd, Weick JK, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol. 1995;13:1880-92. (P1)

8. Armstrong J, Raben A, Zelefsky M, Burt M, Leibel S, Burman C, et al. Promising survival with three-dimensional conformal radiation therapy for non-small cell lung cancer. Radiother Oncol. 1997;44:17-22.

9. Armstrong JG. Three-dimensional conformal radiotherapy. Precision treatment of lung cancer. Chest Surg Clin N Am. 1994;4:29-43.

10. Ball D, Bishop J, Smith J, O'Brien P, Davis S, Ryan G, et al. A randomized phase III study of accelerated or standard fraction radiotherapy with or without concurrent carboplatin in inoperable non-small cell lung cancer: final report of an Australian multi-centre trial. Radiother Oncol. 1999;52:129-36. (C3)

11. Bitran JD, Desser RK, DeMeester T, Shapiro CM, Billings A, Rubenstein L, et al. Combined modality therapy for stage IIIMO non-oat cell bronchogenic carcinoma. Cancer Treat Rep. 1978;62:327-32.

12. Blanke C, Ansari R, Mantravadi R, Gonin R, Tokars R, Fisher W, et al. Phase III trial of thoracic irradiation with or without cisplatin for locally advanced unresectable non-small-cell lung cancer: a Hoosier Oncology Group protocol. J Clin Oncol. 1995;13:1425-9. (C1)

13. Bonner JA, McGinnis WL, Stella PJ, Marschke RF, Jr., Sloan JA, Shaw EG, et al.

The possible advantage of hyperfractionated thoracic radiotherapy in the treatment of locally advanced nonsmall cell lung carcinoma: results of a North Central Cancer Treatment Group Phase III Study. Cancer. 1998;82:1037-48. (C3)

14. Brodin O, Nou E, Mercke C, Linden CJ, Lundstrom R, Arwidi A, et al. Comparison of induction chemotherapy before radiotherapy with radiotherapy only in patients with locally advanced squamous cell carcinoma of the lung. The Swedish Lung Cancer Study Group. Eur J Cancer. 1996;32A:1893-900. (C2)

15. Cheung PC, Mackillop WJ, Dixon P, Brundage MD, Youssef YM, Zhou S. Involved-field radiotherapy alone for early-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2000;48:703-10. (R1)

16. Choi NC, Carey RW, Daly W, Mathisen D, Wain J, Wright C, et al. Potential impact on survival of improved tumour downstaging and resection rate by preoperative twice-daily radiation and concurrent chemotherapy in stage IIIA non-small-cell lung cancer. J Clin Oncol. 1997;15:712-22. (P1)

17. Choy H, Devore RF, 3rd, Hande KR, Porter LL, Rosenblatt P, Yunus F, et al. A phase II study of paclitaxel, carboplatin, and hyperfractionated radiation therapy for locally advanced inoperable non-small-cell lung cancer (a Vanderbilt Cancer Center Affiliate Network Study). Int J Radiat Oncol Biol Phys. 2000;47:931-7.

18. Choy H, Safran H. Preliminary analysis of a phase II study of weekly paclitaxel and concurrent radiation therapy for locally advanced non-small cell lung cancer. Semin Oncol. 1995;22:55-7.

19. Clamon G, Herndon J, Cooper R, Chang AY, Rosenman J, Green MR. Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. J Clin Oncol. 1999;17:4-11. (C1)

20. Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. J Clin Oncol. 1990;8:1543-55.

21. Cox JD, Pajak TF, Asbell S, Russell AH, Pederson J, Byhardt RW, et al. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. Int J Radiat Oncol Biol Phys. 1993;27:493-8. (R1)

22. Cox JD, Scott CB, Byhardt RW, Emami B, Russell AH, Fu KK, et al. Addition of chemotherapy to radiation therapy alters failure patterns by cell type within non-small cell carcinoma of lung (NSCCL): analysis of radiation therapy oncology group (RTOG) trials. Int J Radiat Oncol Biol Phys. 1999;43:505-9.

23. Crino L, Latini P, Meacci M, Corgna E, Maranzano E, Darwish S, et al. Induction chemotherapy plus high-dose radiotherapy versus radiotherapy alone in locally advanced unresectable non-small-cell lung cancer. Ann Oncol. 1993;4:847-51. (C2)

24. Cullen MH, Billingham LJ, Woodroffe CM, Chetiyawardana AD, Gower NH, Joshi R, et al. Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol. 1999;17:3188-94. (C1)

25. Curran WJ, Jr., Werner-Wasik M. Issues in nonoperative management of locally advanced non-small-cell lung cancer. Oncology (Huntingt). 1998;12:60-6.

26. Dautzenberg B, Arriagada R, Chammard AB, Jarema A, Mezzetti M, Mattson K, et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Groupe d'Etude et de Traitement des Cancers Bronchiques. Cancer. 1999;86:265-73. (C1)

27. Debevec M, Bitenc M, Vidmar S, Rott T, Orel J, Strojan P, Kovac V. Postoperative radiotherapy for radically resected N2 non-small-cell lung cancer (NSCLC): randomized clinical study 1988-1992. Lung Cancer. 1996;14:99-107. (C3)

28. Dillman RO, Herndon J, Seagren SL, Eaton WL, Jr., Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst. 1996;88:1210-5. (C1)

29. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med. 1990;323:940-5.

30. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s--meta-analytic comparison of PET and CT. Radiology. 1999;213:530-6.

31. Eagan RT, Ruud C, Lee RE, Pairolero PC, Gail MH. Pilot study of induction therapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) and chest irradiation prior to thoracotomy in initially inoperable stage III M0 non-small cell lung cancer. Cancer Treat Rep. 1987;71:895-900.

32. Eberhardt W, Bildat S, Korfee S. Combined modality therapy in NSCLC. Ann Oncol. 2000;11:85-95.

33. Eberhardt W, Wilke H, Stamatis G, Stuschke M, Harstrick A, Menker H, et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. J Clin Oncol. 1998;16:622-34. (P1)

34. Feng QF, Wang M, Wang LJ, Yang ZY, Zhang YG, Zhang DW, Yin WB. A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. Int J Radiat Oncol Biol Phys. 2000;47:925-9. (C1)

35. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol. 1999;17:2692-9. (C1)

36. Gauden S, Ramsay J, Tripcony L. The curative treatment by radiotherapy alone of stage I non-small cell carcinoma of the lung. Chest. 1995;108:1278-82. (R1)

37. Gollins SW, Burt PA, Barber PV, Stout R. High dose rate intraluminal radiotherapy for carcinoma of the bronchus: outcome of treatment of 406 patients. Radiother Oncol. 1994;33:31-40. (R1)

38. Graham MV, Matthews JW, Harms WB, Sr., Emami B, Glazer HS, Purdy JA. Three-dimensional radiation treatment planning study for patients with carcinoma of the lung. Int J Radiat Oncol Biol Phys. 1994;29:1105-17.

39. Graham PH, Gebski VJ, Langlands AO. Radical radiotherapy for early non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 1995;31:261-6. (R1)

40. Gregor A, Macbeth FR, Paul J, Cram L, Hansen HH. Radical radiotherapy and chemotherapy in localized inoperable non-small- cell lung cancer: a randomized trial. J Natl Cancer Inst. 1993;85:997-9. (C3)

41. Hansen HH, Rorth M. Lung cancer. Cancer Chemother Biol Response Modif. 1991;12:443-59.

42. Hayakawa K, Mitsuhashi N, Saito Y, Nakayama Y, Furuta M, Sakurai H, et al. Limited field irradiation for medically inoperable patients with peripheral stage I non-small cell lung cancer. Lung Cancer. 1999;26:137-42. (R2)

43. Hayman JA, Martel MK, Ten Haken RK, Normolle DP, Todd RF, 3rd, Littles JF, et al. Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase i trial. J Clin Oncol. 2001;19:127-36. (P1)

44. Hazuka MB, Turrisi AT, 3rd, Lutz ST, Martel MK, Ten Haken RK, Strawderman M, et al. Results of high-dose thoracic irradiation incorporating beam's eye view display in non-small cell lung cancer: a retrospective multivariate analysis. Int J Radiat Oncol Biol Phys. 1993;27:273-84.

45. Hilaris BS, Mastoras DA. Contemporary brachytherapy approaches in non-small-cell lung cancer. J Surg Oncol. 1998;69:258-64.

46. Jeremic B, Shibamoto Y, Acimovic L, Djuric L. Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. J Clin Oncol. 1995; 13:452-8. (C1)

47. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. J Clin Oncol. 1996;14:1065-70. (C1)

48. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Hyperfractionated radiotherapy alone for clinical stage I nonsmall cell lung cancer. Int J Radiat Oncol Biol Phys. 1997;38:521-5. (P2)

49. Johnson DH, Einhorn LH, Bartolucci A, Birch R, Omura G, Perez CA, Greco FA. Thoracic radiotherapy does not prolong survival in patients with locally advanced, unresectable non-small cell lung cancer. Ann Intern Med. 1990;113:33-8.

50. Kaskowitz L, Graham MV, Emami B, Halverson KJ, Rush C. Radiation therapy alone for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 1993;27: 517-23. (R2)

51. Kelly K, Mikhaeel-Kamel N. Medical treatment of lung cancer. J Thorac Imaging. 1999;14:257-65.

52. Koukourakis MI, Bahlitzanakis N, Froudarakis M, Giatromanolaki A, Georgoulias V, Koumiotaki S, et al. Concurrent conventionally factionated radiotherapy and weekly docetaxel in the treatment of stage IIIb non-small-cell lung carcinoma. Br J Cancer. 1999;80: 1792-6.

53. Koutaissoff S, Wellmann D, Coucke P, Ozsahin M, Pampallona S, Mirimanoff RO. Hyperfractionated accelerated radiotherapy (HART) for inoperable, nonmetastatic non-small cell lung carcinoma of the lung (NSCLC): results of a phase II study for patients ineligible for combination radiochemotherapy. Int J Radiat Oncol Biol Phys. 1999;45:1151-6. (P2)

54. Krol AD, Aussems P, Noordijk EM, Hermans J, Leer JW. Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation? Int J Radiat Oncol Biol Phys. 1996;34:297-302. (R1)

55. Kubota K, Furuse K, Kawahara M, Kodama N, Yamamoto M, Ogawara M, et al. Role of radiotherapy in combined modality treatment of locally advanced non-small-cell lung cancer. J Clin Oncol. 1994;12:1547-52. (C3)

56. Kupelian PA, Komaki R, Allen P. Prognostic factors in the treatment of node-negative nonsmall cell lung carcinoma with radiotherapy alone. Int J Radiat Oncol Biol Phys. 1996;36:607-13. (R1)

57. Lafitte JJ, Ribet ME, Prevost BM, Gosselin BH, Copin MC, Brichet AH. Postresection irradiation for T2 N0 M0 non-small cell carcinoma: a prospective, randomized study. Ann Thorac Surg. 1996;62:830-4. (C2)

58. Le Chevalier T, Arriagada R, Tarayre M, Lacombe-Terrier MJ, Laplanche A, Quoix E, et al. Significant effect of adjuvant chemotherapy on survival in locally advanced non-small-cell lung carcinoma. J Natl Cancer Inst. 1992;84:58. (C1)

59. Liengswangwong V, Bonner JA. Point: the potential importance of elective nodal irradiation in the treatment of non-small cell lung cancer. Semin Radiat Oncol. 2000;10:308-14.

60. Loprevite M, Favoni RE, de Cupis A, Pirani P, Pietra G, Bruno S, et al. Interaction between novel anticancer agents and radiation in non-small cell lung cancer cell lines. Lung Cancer. 2001;33:27-39.

61. Lukanich JM. Tobacco and public health. Chest. 1999;116:486S-89S.

62. Macbeth FR, Bolger JJ, Hopwood P, Bleehen NM, Cartmell J, Girling DJ, et al. Randomized trial of palliative two-fraction versus more intensive 13- fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Medical Research Council Lung Cancer Working Party. Clin Oncol. 1996;8: 167-75. (C1)

63. Macha HN, Wahlers B, Reichle C, von Zwehl D. Endobronchial radiation therapy for obstructing malignancies: ten years' experience with iridium-192 high-dose radiation brachytherapy afterloading technique in 365 patients. Lung. 1995;173:271-80. (R2)

64. Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis. Cancer. 1995; 76:593-601. (C1)

65. Marom EM, McAdams HP, Erasmus JJ, Goodman PC, Culhane DK, Coleman RE, et al. Staging non-small cell lung cancer with whole-body PET. Radiology. 1999; 212:803-9.

66. Mattson K, Holsti LR, Holsti P, Jakobsson M, Kajanti M, Liippo K, et al. Inoperable non-small cell lung cancer: radiation with or without chemotherapy. Eur J Cancer Clin Oncol. 1988;24:477-82.

67. Mayer R, Smolle-Juettner FM, Szolar D, Stuecklschweiger GF, Quehenberger F, Friehs G, Hackl A. Postoperative radiotherapy in radically resected non-small cell lung cancer. Chest. 1997;112:954-9. (C2)

68. Mehta MP. The contemporary role of radiation therapy in the management of lung cancer. Surg Oncol Clin N Am. 2000; 9:539-61, ix.

69. Mehta MP, Tannehill SP, Adak S, Martin L, Petereit DG, Wagner H, et al. Phase II trial of hyperfractionated accelerated radiation therapy for nonresectable non-small-cell lung cancer: results of Eastern Cooperative Oncology Group 4593. J Clin Oncol. 1998;16:3518-23. (P1)

70. Morita K, Fuwa N, Suzuki Y, Nishio M, Sakai K, Tamaki Y, et al. Radical radiotherapy for medically inoperable non-small cell lung cancer in clinical stage I: a retrospective analysis of 149 patients. Radiother Oncol. 1997;42:31-6. (R1)

71. Morton RF, Jett JR, McGinnis WL, Earle JD, Therneau TM, Krook JE, et al. Thoracic radiation therapy alone compared with combined chemoradiotherapy for locally unresectable non-small cell lung cancer. A randomized, phase III trial. Ann Intern Med. 1991;115:681-6.

72. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest. 1997;111:1710-7.

73. Payne DG. Is preoperative or postoperative radiation therapy indicated in non-small cell cancer of the lung? Lung Cancer. 1994;10 Suppl 1:S205-12.

74. Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. Cancer. 1987; 59:1874-81.

75. Pritchard RS, Anthony SP. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A meta-analysis. Ann Intern Med. 1996;125:723-9. (M1)

76. Reckzeh B, Merte H, Pfluger KH, Pfab R, Wolf M, Havemann K. Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small-cell lung cancer. J Clin Oncol. 1996;14: 1071-6.

77. Rees GJ, Devrell CE, Barley VL, Newman HF. Palliative radiotherapy for lung cancer: two versus five fractions. Clin Oncol. 1997;9:90-5. (C1)

78. Rosell R, Maestre J, Font A, Moreno I, Molina F, Milla A, et al. A randomized trial of mitomycin/ifosfamide/cisplatin preoperative chemotherapy plus surgery versus surgery alone in stage IIIA non-small cell lung cancer. Semin Oncol. 1994;21:28-33.

79. Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB, Jr., Lee JS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst. 1994;86:673-80.

80. Routh A, Hickman BT, Khansur T. Report of a prospective trial--split course versus conventional radiotherapy in the treatment of non small cell lung cancer. Radiat Med. 1995;13:115-9. (C2)

81. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomized multicentre trial. CHART Steering committee. Radiother Oncol. 1999;52:137-48. (C1)

82. Saunders MI. Fractionation and dose in thoracic radiotherapy. Lung Cancer. 1994; 10 Suppl 1:S245-52.

83. Saunders MI, Dische S, Grosch EJ, Fermont DC, Ashford RF, Maher EJ, Makepeace AR. Experience with CHART. Int J Radiat Oncol Biol Phys. 1991;21:871-8.

84. Saunders MI, Rojas A, Lyn BE, Pigott K, Powell M, Goodchild K, et al. Experience with dose escalation using CHARTWEL (continuous hyperfractionated accelerated radiotherapy weekend less) in non-small-cell lung cancer. Br J Cancer. 1998;78: 1323-8. (P1)

85. Sause W, Kolesar P, Taylor SI, Johnson D, Livingston R, Komaki R, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest. 2000;117:358-64.

86. Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. J Natl Cancer Inst. 1995;87: 198-205. (C1)

87. Scarantino CW, McCunniff AJ, Evans G, Young CW, Paggiarino DA. A prospective randomized comparison of radiation therapy plus lonidamine versus radiation therapy plus placebo as initial treatment of clinically localized but nonresectable non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 1994;29:999-1004. (C1)

88. Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, et al. Radiosensitization by cytotoxic drugs. The EORTC experience by the Radiotherapy and Lung Cancer Cooperative Groups. Lung Cancer. 1994;10 Suppl 1:S263-70. (C1)

89. Sculier JP, Paesmans M, Lafitte JJ, Baumohl J, Thiriaux J, van Cutsem O, et al. A randomized phase III trial comparing consolidation treatment with further chemotherapy to chest irradiation in patients with initially unresectable locoregional non-small-cell lung cancer responding to induction chemotherapy. European Lung Cancer Working Party. Ann Oncol. 1999;10:295-303. (C3)

90. Sibley GS. Radiotherapy for patients with medically inoperable Stage I nonsmall cell lung carcinoma: smaller volumes and higher doses--a review. Cancer. 1998;82:433-8.

91. Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys. 1998;40: 149-54. (R2)

92. Sibley GS, Mundt AJ, Shapiro C, Jacobs R, Chen G, Weichselbaum R, Vijayakumar S. The treatment of stage III nonsmall cell lung cancer using high dose conformal radiotherapy. Int J Radiat Oncol Biol Phys. 1995;33:1001-7.

93. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer. Radiother Oncol. 1996;41:41-4. (P2)

94. Slotman BJ, Njo KH, de Jonge A, Meijer OW, Karim AB. Hypofractionated radiation therapy in unresectable stage III non-small cell lung cancer. Cancer. 1993; 72:1885-93. (P1)

95. Slotman BJ, Njo KH, Karim AB. Curative radiotherapy for technically operable stage I nonsmall cell lung cancer. Int J Radiat Oncol Biol Phys. 1994;29:33-7. (P2)

96. Stephens RJ, Girling DJ, Bleehen NM, Moghissi K, Yosef HM, Machin D. The role of post-operative radiotherapy in non-small-cell lung cancer: a multicentre randomized trial in patients with pathologically staged T1-2, N1-2, M0 disease. Medical Research Council Lung Cancer Working Party. Br J Cancer. 1996;74:632-9. (C1)

97. Stout R, Barber P, Burt P, Hopwood P, Swindell R, Hodgetts J, Lomax L. Clinical and quality of life outcomes in the first United Kingdom randomized trial of endobronchial brachytherapy (intraluminal radiotherapy) vs. external beam radiotherapy in the palliative treatment of inoperable non-small cell lung cancer. Radiother Oncol. 2000;56:323-7. (C1)

98. Taylor R, Cumming R, Woodward A, Black M. Passive smoking and lung cancer: a cumulative meta-analysis. Aust N Z J Public Health. 2001;25:203-11.

99. Thomas M, Rube C, Semik M, von Eiff M, Freitag L, Macha HN, et al. Impact of preoperative bimodality induction including twice-daily radiation on tumour regression and survival in stage III non-small-cell lung cancer. J Clin Oncol. 1999; 17:1185. (P1)

100. Trovo MG, Minatel E, Franchin G, Boccieri MG, Nascimben O, Bolzicco G, et al. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 1992;24:11-5. (C2)

101. Trovo MG, Minatel E, Veronesi A, Roncadin M, De Paoli A, Franchin G, et al. Combined radiotherapy and chemotherapy versus radiotherapy alone in locally advanced epidermoid bronchogenic carcinoma. A randomized study. Cancer. 1990;65:400-4.

102. Tubiana M. Radiotherapy in non-small cell lung cancer. An overview. Chest. 1989;96:85S-87S.

103. Turrisi AT, 3rd. Innovations in multimodality therapy for lung cancer. Combined

modality management of limited small-cell lung cancer. Chest. 1993;103:56S-59S.

104. Turrisi AT, 3rd. It's about time, or is it volume, fractionation, or technique? Int J Radiat Oncol Biol Phys. 1996;36:753-5.

105. Williams MD, Sandler AB. The epidemiology of lung cancer. Cancer Treat Res. 2001;105:31-52.

106. Williams TE, Thomas CR, Jr., Turrisi AT, 3rd. Counterpoint: better radiation treatment of non-small cell lung cancer using new techniques without elective nodal irradiation. Semin Radiat Oncol. 2000;10:315-23.

107. Wolf M, Hans K, Becker H, Hassler R, von Bultzingslowen F, Goerg R, et al. Radiotherapy alone versus chemotherapy with ifosfamide/vindesine followed by radiotherapy in unresectable locally advanced non-small cell lung cancer. Semin Oncol. 1994;21:42-7. (C2)

108. Vrdoljak E, Mise K, Sapunar D, Rozga A, Marusic M. Survival analysis of untreated patients with non-small-cell lung cancer. Chest. 1994;106:1797-800.

Overview 1 *Radiotherapy for medically inoperable patients or patients refusing surgery with NSCLC stage I and II.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Cheung 2000 [15] R	Efficacy of RT: 52.5 Gy/20 fr No elective nodal RT	1986–1995 102 pts T1 33.3%, T2 56.9%, T3 8.8%, T4 1% / N0 95.1%, N1 4.9%. 76.5% medically inoperable, 23.5 refused surgery
Gauden 1995 [36] R	Efficacy of RT: 50 Gy/20 fr No elective nodal RT	1985–1992 347 pts stage I 64% medically inoperable 36% refused surgery
Graham 1995 [39] R	Efficacy of RT: 60 Gy/30 fr Elective nodal RT	1979–1985 150 pts stage I, II medically inoperable. 103 pts treated with curative intention: 60 Gy/30 fr; 47 pts got palliative RT
Hayakawa 1999 [42] R	Efficacy of RT 60–81 Gy, 2 Gy/d, 30–40 fr Nodal RT in 10 pts	1976–1994 36 pts stage I medically inoperable
Hayman 2001 [43] P	Feasibility of dose escalation using 3-D planning: 63–102.9 Gy, 2.1 Gy/d	1992–1999 104 pts, 24 stage I, 4 stage II, 43 stage IIIA, 26 stage IIIB, 7 local relapse
Jeremic 1997 [48] P	Efficacy of non accelerated HRT: 69.6 Gy, 1.2 Gy/fr, 2 fr/d, 5.5 w. No elective nodal RT	1988–1993 49 pts stage I 29 medically inoperable 20 refused surgery
Kaskowitz 1993 [50] R	Efficacy of RT 63 Gy, 2 Gy/d nodal RT in 10 pts	1980–1990 53 pts stage I 43 medically inoperable 10 refused surgery

Results	Conclusion/Comments
OS% CSS% at 5 y 16 26.8	Small target volumes. Large series with no elective nodal RT. Low rate (6.6%) of isolated regional relapse. Isolated local relapse 49.2%. The majority of patients relapsed locally and died of their cancer. **R1**
OS% at 5 y 27	Strong correlation between tumour size and survival. The largest series with stage I patients undergoing definitive RT. **R1**
For pts receiving curative RT: **OS at 5 y 14%** OS at 5 y 50% for T1NO, age <70 y, no weight loss For pts receiving palliative RT: **OS at 5 y 5%**	Non randomized comparison between curative and palliative RT in this patient group: better survival in curatively treated patients ($p<0.001$). **R1**
OS% CSS% at 5 y 23 39	4% isolated regional relapse in patients not receiving elective nodal irradiation. Limited number of patients. **R2**
For patients with small tumours the MTD was not reached at 102.9 Gy. For the largest tumours MTD = 65.1 Gy.	Phase I study. The dose not uniformly escalated. Use of Lyman´s NTCP model for predicting the risk for radiation pneumonitis > grade II and to stratify patients in 5 groups. Inclusion ungoing. **P1**
OS% at 5 y OR% CR% 30 83 61	Phase II trial. Small target volumes. Low rate of isolated regional relapses. The majority of failures were local. Low rate of grade III and no grade IV toxicity. Limited number of patients. **P2**
OS% CSS% at 5 y 6 13	Tumour size correlated with survival. Low survival rate compared with other series. **R2**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Krol 1996 [54] R	Efficacy of RT 60 Gy, 3 Gy/d, 3 w split after 30 Gy or 65 Gy/2.5 Gy continuously No elective nodal RT	1978–1992 108 pts stage I 102 medically inoperable 6 refused surgery
Kupelian 1996 [56] R	Efficacy of RT Median dose 63.23 Gy 72% of pts got elective nodal RT	1980–1990 71 pts N0, T1 27%, T2 36%, T3 20%, T4 17% medically inoperable
Morita 1997 [70] R	Efficacy of RT 55–75 Gy, 2 Gy/d 3 Gy/d in 6 pts	1980–1989 149 pts stage I 123 medically inoperable 26 refused surgery
Sibley 1998 [91] R	Efficacy of different RT schedules 50–80 Gy/1.8 Gy/fr, 1 fr/d or 1.6 Gy/fr, 2 fr/d 73% received elective nodal RT	1980–1995 141 pts stage I
Slotman 1994 [95] P	Efficacy of hypofractionated RT: 32 Gy/6 fr 40 Gy/10 fr 48 Gy/12 fr 56 Gy/20 fr elective nodal RT	1984–1990 47 pts stage I 44 medically inoperable 3 refused surgery
Slotman 1996 [93] P	Efficacy of hypofractionated RT: 48 Gy/12 fr No elective nodal RT	1988–1993 31 pts stage I

CHART: continous accelerated hyperfractionated radiotherapy; CR: complete response; CSS: cause specific survival; fr: fraction; HRT: hyperfractionated radiotherapy; LFR:local failure rate; MTD: maximal tolerable dose; ns: not significant; NTCP: normal tissue complication probability; OR: overall response; OS: overall survival; pts: patient(s); RT:radiotherapy; w; week(s); y: year(s)

Results				Conclusion/Comments
OS%	**CSS% at 5 y**	**OR%**	**CR%**	Tumour size correlated to CR and survival. Large series with no elective nodal RT. Low isolated regional recurrence rate (4%). **R1**
15	31	85	46	
OS%	**CSS% at 5 y**			Tumour size correlated to local control and survival. Patients receiving >60 Gy had better local control compared with patients receiving <60 Gy (p=0.019). **R1**
12	32			
OS% at 5 y		**CR%**		Tumour size correlated with CR and survival. **R1**
22.2		38		
OS%	**CSS% at 5 y**			Large series but heterogenous RT regimens. 42% of failures were local only. Uncontrolled lung cancer was the primary cause of death. **R2**
13	32			
OS% at 5 y				Phase II study with dose escalation. Tumour size but not RT dose predictive for local failure. Low toxicity. Limited number of patients. **P2**
15				
Local failure rate 25.5%				
OS% at 3 y		**5 y**		Phase II study. No elective nodal RT. Only 6% regional failure rate. Low OS but high CSS. Most patients died of intercurrent diseases without evidence of cancer. Limited number of patients. **P2**
42		8		
CSS% at 3 y				
76				

Overview 2 *Postoperative radiotherapy in radically resected NSCLC.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Dautzenberg 1999 [26] C	**A:** No further therapy **B:** 60 Gy, 2 Gy/d	1986–1994 728 pts St I = 221, St II = 180, St III = 327 A 373 pts B 355 pts 1:1 randomization
Debevec 1996 [27] C	**A:** No further therapy **B:** 30 Gy, 2.5–3 Gy/d	1988–1992 74 pts pT1–3, pN1–2 A 39 pts B 35 pts 1:1 randomization
Feng 2000 [34] C	**A:** No further therapy **B:** 60 Gy, 2 Gy/d A 134 pts B 162 pts	1982–1995 296 pts 203 stage I, 93 stage III B 43.4 44.9 ns $p<0.01$ 1:1 randomization
Lafitte 1996 [57] C	**A:** No further therapy **B:** 60 Gy, 2 Gy/d	1985–1991 132 pts T2N0 A 72 pts B 60 pts 1:1 randomization

d: day(s); fr: fraction; LRR: locoregional relapse; ns: not significant; OS: overall survival; pts: patient(s); RT:radiotherapy; y: year(s)

Results	Conclusion/Comments
OS% at 5 y A 43 B 30 p=0.002 Subgroup analysis: the detrimental effect of postop RT sign in st I and II but not in st III pts	Detrimental effect of postop RT on survival, was due to an excess of intercurrent mortality in group B, 31% vs 8% in group A, p=0.0001 No effect of postop RT on local recurrence or distant metastatic events. **C1**
No statistical significant difference in survival. (Kaplan-Meier survival curves shown).	Small sample size. Low postop RT dose. No benefit of postop RT in this study. **C3**
OS % at 5 y **LRR%** A 40.5 26.1	Postop RT reduced the incidence of locoregional relapse but not of distant relapse and no significant survival benefit. A numerical trend for better survival in patients with T3, T4 or N1 in group B compared with group A. **C1**
No difference between **A** and **B** according to Kaplan-Meier survival curves but survival figures not given. OS 44.2% in 113 of 132 patients followed ≥5 y.	Homogenous patient population but limited sample size. No benefit of postop RT in this population. **C2**

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Overview 2 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Mayer 1997 [67] C	**A:** No further therapy **B:** 50–56 Gy, 2Gy/d	Inclusion period not stated 155 pts T1–3, N1–2 A: 72 pts B: 83 pts 1:1 randomization
PORT Meta-analysis Trialist Group 1998 [5] M	**A:** No further therapy **B:** Various schedules 30–60 Gy/10–30 fr	1980–1995 2 128 pts, stage I, II, III in 9 randomized trials A: 1 072 pts B: 1 056pts 1:1 randomization
Stephens 1996 [96] C	**A:** No further therapy **B:** 40 Gy/15 fr	1986–1993 308 pts T1–2, N1–2 A: 154 pts B: 154 pts 1:1 randomization

Results			Conclusion/Comments
	OS% at 5 y		OS was not significantly prolonged in N0, N1 or N2 patients. The only factor correlated with survival was pN0. Lower recurrence rate at the bronchial stump ($p<0.01$) in group B. Small sample size and heterogenous pts population. **C2**
A	20.4		
B	29.7 ns		
	OS% at 2 y	**5 y**	Detrimental effect of postop RT on survival. Both local or distant recurrence significantly lower in the control group. The detrimental effect of postop RT was confined to stage I, II. For stage III the difference between A and B was not significant. Postop RT has a detrimental effect in stage I and II and undefined effect in stage III. **M2**
A	55	18	
B	48	12	
	p=0.001		
Median survival, months			Subgroup analysis: No benefit of postop RT in N1 disease. N2 disease trend for better survival in group B at 3 y (A: 21%, B: 36%, 106 pts, p=0.18). Undefined role for postop RT in N2 disease. **C1**
A 19			
B 17.5 In			
OS no sign difference at 2, 3 or 5 y.			

Overview 3 *Altered fractionation schedule with or without chemotherapy in patients, medically inoperable or with locally advanced unresectable NSCLC.*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Ball 1999 [10] C	Benefit of HART and CHT co **A:** 2 Gy/fr, 1 fr/d, 60 Gy/6 w **B:** 2Gy/fr, 2 fr/d, 60 Gy/3 w **C:** RT as A + CHT co w 1 + 5 **D:** RT as B + CHT co w 1 1 + 5	1989–1995 204 pts 44 medically inoperable stage I, II, III and 160 pts unresectable stage III. A 42 pts B 36 pts C 41pts D 41 pts 1:1:1:1 randomization
Bonner 1998 [13] C	Benefit of HART and CHT co **A:** 2 Gy/fr, 1 fr/d, 60 Gy/6 w **B:** 1.5 Gy/fr, 2 fr/d, 60 Gy/6 w, 2 w split after 30 Gy **C:** RT as B + CHT co	1992–1993 110 pts unresectable stage III, 99 pts eligible A 34 pts B 33 pts C 32 pts 1:1:1 randomization
Cox 1993 [21] R	To assess the impact of prolonged RT duration on survival	1983–1989 1 244 pts medically inoperable stage I, II, III or unresectable stage III included in 3 randomized trials RTOG 8311, 8321 and 8403.
Koutaissoff 1999 [53] P	Efficacy of HART in a medically compromised pts population. HART 1.5 Gy/fr, 2 fr/d, 63 Gy/29 d	1989–1994 23 pts medically compromised with stage I, II, III not eligible for surgery or chemo-radiotherapy
Mehta 1998 [69] P	Efficacy of HART in unresectable stage III pts HART 1.5–1.8 Gy/ fr, 3 fr/d, 36 fr, 57.6 Gy	1993–1995 30 pts unresectable stage III Median survival 13 m

CHT ref [10]: Carboplatin + etoposide.
CHT ref [13]: Cisplatin + etoposide d 1–3, w 1 + 5.
CHARTWEL: continous hyperfractionated accelerated radiotherapy week-end less; co: concomitant;
CR: complete response; CSS: cause specific survival; fr: fraction; HART: hyperfractionated accelerated radiotherapy;
HRT: hyperfractionated radiotherapy; m: month(s); ns: not significant; OR: overall response; OS: overall survival;
pts: patient(s); RT:radiotherapy; SCC: squamous cell carcinoma; w; week(s); y: year(s)

Results	Conclusion/Comments
All patients: Median survival 15.7 months OS at 2 yr 31% No statistical difference between A, B, C, D but numerical trend for better survival in C: OS at 2 yr 41%	No survival benefit but increased esophageal toxicity with HART. Underpowered study with only 40 pts/arm. **C3**
OR% A 38 B 64 p=0.04 C 41 OS as shown by Kaplan-Meier curves, no significant differences between A, B, C	No significant survival benefit with HART or CHT added to HART. Numerical trend for longer survival in B and C. In the subgroup with non squamous histology HART (B and C) was associated with better OS (p=0.02). Underpowered study with only 0.35 power to observe survival differences at a P=0.05 level. **C3**
The majority of delays were recorded with HRT and increased when higher doses were prescribed. OS for HRT patients was higher in patients treated "per protocol" compared with HRT with unplanned delays.	Interruptions delaying completion of planned HRT have adverse effect on survival (P=0.016). The detrimental effect increased in patients with good PS, little weight loss and <N3. **R1**
OR% **OS% at 2 y** 48 39 Median survival 16.8 m	Phase II trial. This HART regimen feasible in medically frail patients and followed by low toxicity. **P2**
OR% **OS% at 1 y** 54 57	Phase II trial. This HART regime feasible and well tolerated. Response and survival comparable with results from trials with chemo-radiotherapy in this group of patients. **P1**

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Overview 3 *continued*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Routh 1995 [80] C	Morbidity and survival with continuous and split course RT. **A:** RT 55 Gy/1.8–2 Gy/d **B:** RT 60 Gy/1.8–2 Gy/d, split 10–14 days after 18 fr	1982–1988 273 pts medically inoperable stage I, II, III or unresectable stage III A 159 pts B 114 pts randomization 1:1
Saunders 1998 [84] P	Efficacy of CHARTWEL in medically compromised pts CHARTWEL 1.5 Gy/fr, 3 fr/d, 54–60 Gy/16–18 d	1990–1996 64 pts medically inoperable stage I, II, III or unresectable stage III
Saunders 1999 [81] C	Benefit of CHART **A:** 2 Gy/fr, 1 fr/d, 60 Gy/6 w **B:** 1.5 Gy/3 fr/d, 54 Gy/12 d, 6 h between fr.	1990–1995 563 pts/203 stage I, II A 225 pts/ 82 stage I, II B 338 pts/ 121 stage I, II SCC A: 84%, B: 81% 2:1 randomization
Sause 1995, 2000 [85,86] C	HRT and neoadj CHT **A:** RT 60 Gy/2 Gy/d **B:** Neoadj CHT + same RT as A **C:** 1.2 Gy/fr, 2 fr/d, 69.6 Gy	1989–1992 490 pts 26 stage II, 206 IIIA, 226 IIIB 458 eligible A 152 pts B 152 pts C 154 pts 1:1:1 randomization
Slotman 1993 [94] P	Hypofractionated RT in pts with unresectable stage III: **A:** 4–5 Gy/fr to 20 Gy/1 w, 1 wsplit, 4–5 Gy/fr to 20 Gy/1 w , total dose 40 Gy/3 w **B:** 5–6 Gy/fr, 2 fr/w to 30–32 Gy/3 w **C:** 8 Gy/fr, 1 fr/w, 24 Gy/3 w	1986–1989 306 pts unresectable stage III A 92 pts B 129 pts C 85 pts

CHT ref [85,86]: Cisplatin + vinblastine

Results	Conclusion/Comments
Median survival, m A 11 B 11.6 ns **OS% at 3 y** A 7 B 7	The imbalance between A and B regarding patient number caused by problems with patient compliance, several patients did not return after split to receive the 2nd RT course of 17 fr. Poor survival in both arms. No advantage or disadvantage of split course RT in this material. Morbidity is stated to be less in B but it is not shown how it was measured. **C2**
Acute esophagitis but not pnemonitis more common in pts treated to 60 Gy.	Phase I study. CHARTWEL feasible and dose escalation from 54 to 60 Gy safe. More acute esophageal toxicity with higher dose but no increase of late toxicity. **P1**
OS at 2 y **All pts** **SCC** **nn SCC** A 21 20 21 B 30 33 27 p=0.008 p=0.0007 ns	The benefit of CHART was confined to SCC patients in all stages including stage I,II. The majority of the patients were SCC, the number of non SCC patients being only 102. CHART was associated with higher rate of acute radiation induced esophagitis (grade III/IV A: 19% B: 3%) but not pneumonitis (A: 65% B: 56%) **C1**
Median survival, m A 11.4 B 13.2 C 12 **OS% at 2 y** **5 y** A 21 5 B 32 8 C 24 6 A vs B p=0.04	No significant survival advantage for HRT compared with conventional RT. Survival significantly improved with CHT neoadj + RT compared to RT alone. **C1**
OS% at 2 y **5 y** 13 2 Median survival 8.2 months In pts with stage IIIA, OS in group A. was significantly longer compared to group B and C.	Phase II study with 3 different hypofractionated RT schedules. Low OS in this patient material with exception of pts. with stage IIIA, treated in group A. Median survival 11.4 months, OS at 2 y 22%, OS at 5 y 7% (these results being comparable with results from trials with conventional RT). **P1**

Overview 4 *Neoadjuvant chemotherapy plus radiotherapy versus radiotherapy alone or chemotherapy alone.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Brodin 1996 [14] C	Benefit of CHT neoadj **A:** RT 56 Gy, 2 Gy/d, split 2 w after 38 Gy **B:** CHT neoadj + same RT as A	1984–1989 327 pts, 58 medically inoperable stage I,II, 200 IIIA, 18 IIIB, 26 unclassified 302 eligible A 154 pts B 148 pts 1:1 randomization
Crino 1993 [23] C	Benefit of CHT neoadj **A:** RT 56 Gy, 2 Gy/d **B:** CHT neoadj + same RT as A	1984–1989 66 pts stage IIIA/IIIB, 61 eligible A 33 pts B 33 pts 1:1 randomization
Cullen 1999 [24] C	Benefit of CHT neoadj **A:** RT >40 Gy/15 fr **B:** CHT neoadj + same RT as A Received RT median 50 Gy (40–60 Gy)/ 15 fr (10–20)	1988–1996 461 pts stage IIIA/IIIB, 446 eligible A 223 pts B 223 pts 1:1 randomization
Dillman 1996 [28] C CALGB 8433	Benefit of CHT neoadj **A:** RT 60 Gy, 2 Gy/d **B:** CHT neoadj + same RT as A	1984–1987 180 pts stage IIIA/IIIB, 155 eligible A 77 pts B 78 pts 1:1 randomization

CHT ref [14]: Cisplatin + etoposide
CHT ref [23]: Cisplatin + etoposide
CHT ref [24]: Mitomycin + ifosfamide + cisplatin (MIP)
CHT ref [28]: Cispaltin + vinblastine
BSC: best supportive care; CHT: chemotherapy; co: concomitant; CR: complete response; CSS: cause specific survival; fr: fraction; HRT: hyperfractionated radiotherapy; m: month(s); neoadj: neoadjuvant; ns: not significant; OR: overall response; OS: overall survival; pts: patient(s); QoL: quality of life; RT:radiotherapy; w; week(s); y: year(s)

Results	Conclusion/Comments
OS% at 2 y Median survival, m A 17 10 B 21 ns 11	The pts population included both medically inoperable early stage and unresectable locally advanced pts. Trend for improved OS, trend for improved local control (p=0.08) and decreased distant metastatic events (p=0.1) in group B pts. **C2**
OS% at 2 y Median survival, w A 14 36 B 30 52 p=0.11	The pts population was homogenous but the sample size too limited to detect survival differences. Strong trend for improved survival in pts treated with CHT + RT. Underpowered study failing to reach significance in results. **C2**
OS% at 2 y Median survival, m A 16 9.7 B 24 11.7 p=0.14	This trial was parallel with another trial including 351 pts, stage IIIB/IV, randomized between MIP or BSC. When both trials were analysed together the pts receiving MIP had significantly improved survival (P=0.01). Radiotherapy was administered according to different doses and schedules in different institutions in UK. QoL assessed in 67 pts and was significantly improved in B compared to A (P=0.0002). **C1**
OS% at 2 y 7 y Median survival, m A 13 6 9.6 B 26 13 13.6 p=0.012	One of the few studies presenting data beyond 5 y. Homogenous pts population with PS =0,1 and no spread to supraclavicular nodes. Significant survival improvement in pts treated with CHT + RT. This was not a large randomized trial but had a great impact in establishing CHT + RT as treatment for pts with unresectable, locally advanced tumour and good PS. **C1**

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Overview 4 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Gregor 1993 [40] C	Benefit of CHT neoadj **A:** palliative RT ≤ 30 Gy **B:** RT 50 Gy/20 fr **C:** CHT neoadj + same RT as B	1984–1989 118 pts stage IIIA/IIIB, 117 eligible A 39 pts B 39 pts C 39 pts 1:1:1 randomization
Le Chevalier 1992 [58] C CEBI trial	Benefit of CHT neoadj **A:** RT 65 Gy, 2.5 Gy/d **B:** CHT neoadj + RT 60 Gy, 2.5 Gy/d B 176 pts	1984–1987 353 pts stage IIIA/IIIB, A 177 pts p=0.02 1:1 randomization
Kubota 1994 [55] C	CHT neoadj + RT vs CHT alone. **A:** CHT **B:** CHT neoadj + RT 50–60 Gy, 2 Gy/d	1986–1988 92 pts stage IIIA/IIIB first randomized to PVd or PVdM or PE alt MVd After 2 CHT cycles 63 patients still stage III randomized to A or B A 31 pts B 32 pts 1:1 randomization
Marino 1995 [64] M	Benefit of CHT neoadj or CHT co **A:** RT **B:** CHT neoadj + RT or CHT co + RT	Inclusion period not stated. 1 887 pts. stage IIIA/IIIB in 15 randomized trials.
NSCLC Collaborative Group 1995 [3] M	Benefit of CHT neoadj **A:** RT **B:** CHT neoadj + RT	1968–1988 3 033 pts. stage IIIA/IIIB in 22 randomized trials. 1 780 pts. in 11 randomized trials using cisplatin-based CHT.

CHT ref [40]: Cisplatin + vindesine
CHT ref [58]: Cisplatin + cyclophosphamide + vindesine + lomustine
CHT ref [55]: Cisplatin + vinblastine (PVd) ± mitomycin (PVdM) or cisplatin + etoposide(PE) alternative with mitomycin + vindesine (MVd)

Results			Conclusion/Comments
	OS% at 2 y	**Median survival, w**	This trial was closed prematurely due to poor accrual and the sample size is too limited to detect OS differences. The positive trend for improved survival with active treatment (groups B and C) did not reach statistical significance. No impact of CHT added to RT in this study. **C3**
A	15	34	
B	20	53	
C	20	52	
	ns		
	OS% at 2 y	**Median survival, m**	Large randomized trial showing significant survival improvement in pts treated with CHT + RT. Careful assessment of local control which was poor in both arms. Decreased distant metastases rate in B compared to A (P<0.001). **C1**
A	14	10	
B	21	12	
	OS% at 2 y	**Median survival, d**	This small trial used double randomization. The aim of the second randomization was to assess the benefit of RT added to CHT compared to CHT alone. Albeit the sample size was limited a survival benefit at 2 and 3 y could be detected in pts receiving RT after induction CHT compared with CHT alone. **C3**
A	9	447	
B	36	461	
	p=0.016		
Reduction of mortality in CHT neoadj + RT or CHT co + RT compared to RT alone: at 2 y with 18% (non cisplatin-based CHT) 30% (cisplatin-based CHT)			This meta-analysis is not based on individual data and includes trials testing both neoadjuvant and concomitant CHT. The majority of pts were included in trials with neoadjuvant treatment. The analysis shows a small survival benefit at 1 and 2 but not 3 and 5 y. **M2**
Increase of OS in CHT + RT compared to RT: at 2 y with 3% at 5 y with 2% p=0.006 for cisplatin-based CHT at 2 y with 4% at 5 y with 2% p=0.005			Comprehensive assessment of CHT + RT vs RT based on individual updated data from pts included in randomized trials (published and unpublished). This meta-analysis shows a small but significant survival advantage for addition of CHT to RT. The strongest evidence comes from trials using cisplatin. Alkylating agents had no conclusive effect. **M1**

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Overview 4 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Pritchard 1996 [75] M	Benefit of CHT neoadj or CHT co **A:** RT **B:** CHT neoadj + RT or RT + CHT co	Inclusion period not stated. 2 589 pts. stage IIIA/IIIB in 14 randomized trials published between 1987 and 1995. 8 trials employed CHT neoadj + RT
Sause 1995 [85,86] C	Benefit of CHT neoadj vs RT or HRT alone **A:** RT 60 Gy, 2 Gy/d **B:** CHT neoadj + RT 60 Gy, 2 Gy/d **C:** HRT 69.6 Gy, 1.2 Gy/fr, 2 fr/d	1989–1992 490 pts 26 stage II, 206 IIIA, 226 IIIB 458 eligible A 152 pts B 152 pts C 154 pts 1:1:1 randomization
Sculier 1999 [89] C	CHT neoadj + RT vs CHT alone **A:** CHT **B:** CHT neoadj + RT	1989–1996 Pts achieving response after 3 CHT cycles (115/462) were randomized A 60 pts B 55 pts 1:1 randomization
Wolf 1994 [107] C	CHT neoadj added to RT + CHT co **A:** RT 50 Gy, 2 Gy/d + CHT co **B:** CHT neoadj + RT + CHT co same as in A	1986–1989 85 pts stage IIIA/IIIB, 78 eligible A 41 pts B 37 pts 1:1 randomization

CHT ref [85,86]: Cisplatin + vinblastine
CHT ref [89]: Mitomycin + ifosfamide + cisplatin(MIP)
CHT ref [107]: CHT co = Cisplatin weekly; CHT neoadj = ifosfamide + vinblastine.

Results	Conclusion/Comments
Reduction of mortality in CHT neoadj + RT or RT + CHT co compared to RT alone: at 2 y with 13% at 3 y with 17%	This meta-analysis is not based on individual data and includes trials testing both neoadjuvant and concomitant CHT. The majority of pts were included in trials with cisplatin/carboplatin-based CHT (11 trials). The analysis shows a small but significant survival benefit at 1, 2 and 3 y. **M1**
OS% at 2 y Median survival, m A 21 11.4 B 32 p=0.04 13.2 C 24 12.0	The majority of the pts had unresectable tumour stage III. The same CHT and RT regime as in ref 75. Survival significantly improved with CHT + RT compared to RT alone. The superiority of CHT + RT compared to RT confirms the results of ref 75. No significant survival advantage for HRT compared with conventional RT. **C1**
OS% at 2 y Median survival, w A 18 42 B 22 54 ns	This study investigated the role of consolidating RT in responders to CHT. RT was compared to further CHT. Albeit significant better local control with CHT + RT compared with CHT alone (p=0.0007) no significant survival advantage for the combined modality. However, the combined modality group showed a positive trend for improved survival. Limited sample size. The results cannot be extrapolated to a chemonaive population. **C3**
OS% at 2 y Median survival, m A 12 9.0 B 24 13.7 p=0.016	Albeit limited sample size significantly improved survival with induction CHT. In both groups pts received concomitant low dose weekly cisplatin together with RT. **C2**

Overview 5 *Radiotherapy with concomitant chemotherapy [10,12,13] neoadjuvant chemotherapy and radiotherapy vs neoadjuvant chemotherapy and radiotherapy with concomitant chemotherapy [19], radiotherapy with neoadjuvant chemotherapy vs radiotherapy with concomitant chemotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Ball 1999 [10] C	See overview 3	
Bonner 1998 [13] C	See overview 3	
Blanke 1995 [12] C	Benefit of CHT co **A:** RT 60–65 Gy, 1.8–2 Gy/d **B:** RT same as A + CHT co	1986–1992 240 pts.: 19 medically inoperable stage I,II 221 unresectable IIIA/IIIB, 215 eligible A 123 pts B 117 pts 1:1 randomization
Clamon 1999 [19] C	Benefit of CHT co added to CHT neoadj + RT **A:** CHT neoadj + RT 60 Gy, 2 Gy/d **B:** CHT neoadj + RT same as A + CHT co	1991–1996 283 pts. unresectable IIIA/IIIB, 252 eligible A 137 pts B 146 pts 1:1 randomization
Furuse 1999 [35] C	Benefit of CHT co vs CHT neoadj **A:** CHT neoadj + RT 56 Gy, 2 Gy/d **B:** RT 56 Gy, 2 Gy/d + CHT co. 10 d split after 28 Gy	1992–1994 320 pts. unresectable IIIA/IIIB, 314 eligible A 158 pts B 156 pts 1:1 randomization
Jeremic 1995 [46] C	Benefit of CHT co with HRT **A:** HRT 64.8 Gy, 1.2 Gy/fr, 2 fr/d **B:** HRT same as A + CHT co[1] **C:** HRT same as A + CHT co[2]	1988–1989 169 pts. unresectable IIIA/IIIB, A 61 pts B 52 pts C 56 pts 1:1:1 randomization

CHT ref [12]: Cisplatin every 3rd week during RT
CHT ref [19]: CHT neoadj: Cisplatin + vinblastine; CHT co: carboplatin weekly during RT
CHT ref [35]: CCHT neoadj = CHT co: Cisplatin + vindesine + mitomycin
CHT ref [46]: CHT co[1]:Carboplatin + etoposide weekly; CHT co[2]: Carboplatin + etoposide once week 1, 3, 5
CHT: chemotherapy; fr: fraction; HRT: hyperfractionated radiotherapy; m: month(s) ns: not significant;
OS: overall survival; pts: patient(s); RT:radiotherapy; w; week(s); y: year(s)

Results	Conclusion/Comments
OS% at 2 y **Median survival, w** A 13 46 B 18 43 ns	Cisplatin concomitant with RT does not improve survival compared with RT alone Response, local control, distant metastases rate were similar in the two groups. **C1**
OS% at 2 y **Median survival, m** A 26 13.5 B 29 13.4 ns	Carboplatin concomitant with RT does not improve survival compared with RT alone. Both groups received the same neoadjuvant CT. Response, local control, distant metastases rate were similar in the two groups. **C1**
OS% at 2 y **Median survival, m** A 27,4 13.3 B 34,6 16.5 p=0.039	Cisplatin-based multidrug CHT concomitant with RT significantly improved survival compared to the same CHT given neoadjuvantly. **C1**
OS% at 2 y 5 y **Median survival, m** A 25 4.9 8 B 35 21 18 C 27 16 13 A vs B p=0.0027 A vs C p=0.17 B vs C p=0.14	Weekly CHT concomitant with HRT (group B) significantly improved survival compared with HRT alone. The intermittent CHT schedule (group C) did not have the same effect as the weekly schedule, not significantly influencing OS. The improved survival in group B was associated with improved local control. **C1**

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Overview 5 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Jeremic 1996 [47] C	Benefit of CHT co with HRT. **A:** HRT 69.6 Gy, 1.2 Gy/ fr, 2 fr/d **B:** HRT same as A + CHT co	1990–1991 131 pts. unresectable IIIA/IIIB, A 66 pts B 65 pts 1:1 randomization
Marino 1995 [64] M	See overview 4	
Pritchard 1996 [75] M	See overview 4	
Scarantino 1994 [87] C	Benefit of radiosensitizing agent **A:** RT 55–60 Gy, 1.8 Gy/d **B:** Same RT as A + Ionidamine daily during RT	1986–1991 310 pts. medically inoperable stage II, unresectable IIIA/IIIB, A 152 pts B 158 pts 1:1 randomization
Schaake-Koning 1994 [88] C	Benefit of CHT co **A:** RT 55 Gy, 2.5–3 Gy/d split 2 w after 30 Gy **B:** RT same as A + CHT co[1] **C:** RT same as A + CHT co[2]	1984–1989 331 pts. 63 medically inoperable stage I/II, 268 unresectable IIIA/IIIB, 307 eligible A 114 pts B 107 pts C 110 pts 1:1:1 randomization
Trovo 1992 [100] C	Benefit of CHT co **A:** T 45 Gy/15 **B:** RT same as A + CHT co	1987–1991 173 pts. unresectable IIIA/IIIB, 169 eligible A 88 pts B 85 pts 1:1 randomization

CHT ref [47]: CHT co: Carboplatin etoposide daily during RT
CHT ref [88]: CHT co[1] = Cisplatin once daily; CHT co[2]: cisplatin once weekly
CHT ref [100]: CHT co = cisplatin once daily

Results	Conclusion/Comments
OS% at 4 y Median survival, m A 9.1 14 B 23.0 22 p=0.021	Daily CHT concomitant with HRT significantly improved survival compared with HRT alone. The improved survival in group B was associated with improved local control. **C1**
Median survival, d A 326 B 392 OS at 2 and 3 y as shown by Kaplan-Meier no statistical difference between A and B.	Single agent Lo given in 3 doses daily concomitant with RT does not improve survival compared with RT alone Response, local control, distant metastases rate were similar in the two groups. **C1**
OS% at 2 y A 13 B 26 C 19 A vs B p=0.009 A vs C ns	Single agent cisplatin given in a low dose daily schedule concomitant with RT significantly improved survival compared with RT alone. The same single agent given in a weekly schedule produced a trend for improved survival, not reaching statistical significance. The improved survival was associated with improved local control. The distant metastases rate was not affected by the addition of CHT to RT. **C1**
OS% at 2 y Median survival, m A 20 10.3 B 17 10 .0 ns	Single agent cisplatin daily concomitant with RT does not improve survival compared with RT alone. Response, local control, distant metastases rate were similar in the two groups. **C2**

Overview 6 *Chemo-radiotherapy before surgery in NSCLC (tri-modality treatment).*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Albain 1995 [7] P SWOG 8805	Chemo-radiotherapy + S in primarily unresectable stage III NSCLC RT 45 Gy, 1.8 Gy/d + CHT co + S	1988–1992 126 pts 75 stage IIIA(N2) 51 stage IIIB
Choi 1997 [16] P	Chemo-radiotherapy + S in primarily unresectable stage III NSCLC RT 42 Gy, 1.5 /fr, 2 fr/d + CHT co + S	1988–1995 42 pts IIIA(N2)
Eberhardt 1998 [33] P	Chemo-radiotherapy + S in primarily unresectable stage III NSCLC CHT neoadj + RT 45 Gy, 1.5/fr, 2 fr/d + CHT co + S	1991–1994 94 pts 52 stage IIIA(N2) 42 stage IIIB stage III B 45%
Thomas 1999 [99] P	Chemo-radiotherapy + S in primarily unresectable stage III NSCLC CHT neoadj +RT 45 Gy, 1.5 Gy/fr, 2 fr/d + CHT co + S	1985–1991 54 pts 25 stage IIIA(N2) 29 stage IIIB

CHT ref [7]: CHT co: Cisplatin + etoposide
CHT ref [16]: CHT co: Cisplatin + vinblastine + 5 fluorouracil
CHT ref [33]: CHT neoadj and CHT co: Cisplatin + etoposide
CHT ref [99]: CHT neoadj: ifosfamide + carboplatin + etoposide; CHT co: Carboplatin + vinblastine
CHT: chemotherapy; co: concomitant; fr: fraction; neoadj: neoadjuvant; OS: overall survival; OR: overall response; pOR: pathologic overall response; pCR – pathologic complete response; pR: pathologic response rate; RT: radiotherapy; S: surgery; SD: stable disease; y: year(s)

Results	Conclusion/Comments
OR% p **OR% p** **CR%** 59 72 15 Resectability stage III A, 76%, stage III B 63% **OS% at 3 y** Stage IIIA 27 Stage IIIB 24	Phase II study. Trimodality treatment feasible. High resectability rate. Clear biological effect of chemo-radiotherapy: 44% either pCR or microscopic residual disease. Presurgical evaluation had low predictable value: of 26 patients classified as SD after CHT and resected 12 (46%) had either pCR or only microscopic residual disease. pCR in mediastinum predicted for outcome. **P1**
OR% **pCR %** **OS% at 5 y** 74 9.5 37 Complete resection possible in 80%	Phase II study. pCR in mediastinum (down-staging from N2 to N0/1) 67%. Down-staging from N2 to N0 33.5%. High down-staging rate and high OS in this population (IIIAN2). **P1**
OR% **pCR%** 64 26 Complete resection 60% stage III A 60%, **OS% at 3 y 5 y** Stage IIIA 36 31 Stage IIIB 26 26	Phase II study. High pCR. Clear biological effect of chemo-radiotherapy: 40% either pCR or microscopic residual disease. OS similar to ref 101. **P1**
OR% **pCR%** 69 17.5 Complete resection 63% **OS% at 3 y** Stage IIIA 35 Stage IIIB 26	Phase II study. Major pR (>90% regression of tumour) 50%. OS similar to ref 101. **P1**

Overview 7 *Palliative radiotherapy for control of symptoms related to intrathoracic tumour.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Gollins 1994 [37] R	Efficacy of BRT to palliate symptoms BRT HDR 10–20 Gy x 1	1988–1992 406 pts. stage III/IV a. 324 received BRT as primary RT b. 65 previously treated with RT, relapsed and received BRT c. 17 treated treated with concurrent RT and BRT
Macbeth 1996 [62] C	Different RT schedules for symptom palliation **A:** 8.5 Gy x 2, 1 week between fractions **B:** 3 Gy x 13	1989–1992 509 pts with good PS unresectable stage III, ineligible for curative RT or stage IV A 255 pts B 254 pts 1:1 randomization
Macha 1995 [63] R	Efficacy of BRT to palliate symptoms BRT HDR 5–7.5 Gy x 1–6	1983–1993 346 pts, stage III/IV 1983–1986 124 pts: 5–7.5 Gy x 1–6 1986–1993 121 pts: 5 Gy x 3 43 pts: 5 Gy x 2 35 pts: 5 Gy x 1

BRT: intraluminal palliative brachytherapy; HDR: high dose rate; ns: not significant; OS: overall survival; PS: performance status; RT:radiotherapy; spt: symptom(s);

Results	Conclusion/Comments
Palliation of spt 60–92%: stridor 92% hemoptysis 88% cough 62% dyspnea 60% 8% fatal hemoptysis	Large retrospective analysis. Homogenous BRT (single fraction 10–20 Gy). Low frequency of lethal complications. BRT well tolerated in terms of acute and late morbidity. High rate of symptom palliation. **R1**
Median survival, months A 7 B 9 p=0.03 Numerically higher rate of spt palliation in A compared to B.	This trial included good PS patients. For stage III patients, the reason for not giving RT with curative intent was locally too extensive tumour. Palliation of spt assessed by clinicians and patients. Schedule B resulted in longer OS but the regime A produced a more rapid palliation of symptoms. **C1**
Palliation of spt 66% 21% fatal hemoptysis	Large retrospective analysis. Patients included in several different treatment protocols. The high rate of fatal hemoptysis was associated with poor control of local disease and thus not a true figure for treatment complications. **R2**

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Overview 7 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
MRC 1992 [2] C	Different RT schedules for symptom palliation **A:** 8.5 Gy x 2, 1 week between fractions **B:** 10 Gy x 1	1988–1989 235 pts with poor PS unresectable stage III or stage IV > A 117 pts B 118 pts 1:1 randomization
Rees 1997 [77] C	Different RT schedules for symptom palliation **A:** 8.5 Gy x 2, 1 week between fractions **B:** 2.5 Gy x 5	1989–1993 216 pts stage III or stage IV A 111 pts B 105 pts 1:1 randomization
Stout 2000 [97] C	RT compared with BRT, palliation and OS **A:** T 3 Gy x 10 **B:** BRT HDR 15 Gy x 1	1989–1993 99 pts. stage III/IV with cough, dyspnea, hemoptysis due to endobronchial tumour component and other symptoms: chest pain, anorexia, tiredness A 50 pts B 49 pts

Results	Conclusion/Comments
Palliation for cough, haemoptysis, chest pain, anorexia and dysphagia similar in A and B with no significant differences. **Median survival, days** A 122 B 100 ns	This trial included poor PS pts. (different population compared with the first MRC trial reported 1991). Carefully assessed palliation by both clinicians and patients. The simplified regimen with a single 10 Gy fraction had similar efficacy as the 2 fraction regimen, previously (MRC 1991) found to be equivalent to the classical palliative regimen 3 Gy x 10. **C1**
No differences between these schedules.	No differences between these schedules but lower palliative efficacy compared with the MRC trials. The only symptom that was improved in over 50% of patients was hemoptysis. Hemoptysis and chest pain appeared to be the best indications for treatment. The relief of other symptoms was disappointing in both degree and duration. **C1**
Palliation of spt: Clinician assessment: non significant trend for better palliation in A compared with B, P=0.09. Patient assessment significant better palliation in A compared with B, p=0.029. **Median survival, days** A 287 B 250 p=0.042	RT had a better palliative effect of symptoms associated with the bulk of tumour: (chest pain, anorexia, tiredness) and was not inferior to BRT to palliate symptoms associated with the endobronchial component. RT preferred to BRT as initial palliative treatment because of better palliation and OS. **C1**