SECTION III
PATIENT SUPPORT AND DEFINITIVE TREATMENT

4. SUPPORTING THE PATIENT DURING DIAGNOSIS AND TREATMENT

4.1 INFORMATION PROVISION

The diagnosis and treatment of lung cancer is a major stressful life event for every individual afflicted and requires an adaptive adjustment to sustain quality of life. Attention to information provision and communication with the patient, to their psychological adaptation and their social needs are fundamental dimensions of care that will enhance their quality of life while striving to prolong survival.

Consumer satisfaction surveys of patients with cancer repeatedly identify information provision as a major source of unmet needs[1]. A meta-analysis of educational interventions in cancer has shown that the provision of adequate information is related to increased psychological wellbeing[2]. Effective communication skills ensure that this information is clearly explained and understood[3,4].

Studies have shown that only part of the initial consultation is remembered[5]. Therefore clinicians need to recognise that the integration of information is a gradual process that requires both time and the opportunity to ask questions at subsequent visits. It is not necessary to make treatment decisions at the initial consultation unless the patient clearly chooses to do so. For non-English patients, professional interpreter services should be used and use of family members as interpreters avoided.

When breaking bad news, two points are particularly important: firstly, care should be taken to deliver the information in language that the patient understands and secondly, appropriate support, including the attendance of significant others, if desired by the patient, should be provided. Tape recording of such sessions should be routinely offered[6]. The NHMRC recommends the following approach for breaking bad news, adapted from The Cancer Council New South Wales[1]:

- give bad news in a quiet, private place
- allow enough uninterrupted time in the initial meeting
- assess the individual's understanding
- provide information simply and honestly
- encourage individuals to express their feelings
- respond to individual's feelings with empathy
- give a broad time-frame for the prognosis
- avoid the notion that nothing can be done
- arrange a time to review the situation
- discuss treatment options
- offer assistance to tell others
- provide information about support services
- provide written information
- offer a tape recording of the session.

In our society, most patients wish to be fully informed of all available information, and usually want a close relative or friend present during this interview[7]. In general, cancer patients should be invited to guide the clinician about the level of detail they wish to receive and their desire for active involvement in decision making[8]. Discussion of the actions that can be taken and what the diagnosis means, are at least, if not more, important than the disclosure of the initial diagnosis[9]. The clinician's choice of words is critical, as being deliberately vague or using euphemisms can significantly impair communication[10].

Clinicians should review both the patient's understanding of what they have been told and their reaction to this news, as a means of increasing integration of this information and providing emotional support. Patients are entitled to make their own decisions about treatments or procedures, but need adequate information on which to base these decisions. One study of patients with lung cancer found that 29% perceived a discrepancy between their desired role in decision making and their actual role[11]. Nearly two thirds sought an active, collaborative decision making style[11]. Clinicians should provide information in a form and manner that helps the patient to understand the treatment options available, and which is tailored to the patient's circumstances, personality, level of education and understanding, expectations, fears, beliefs, values and cultural background[12].

In regard to prognosis, a study of patients with metastatic incurable cancer revealed that the information most sought by patients included longest survival time with treatment, five-year survival rates, and average survival. Words and numbers were preferred to graphs[13].

There can be difficulty in comparing results between studies as the outcome may be reported in different ways. For instance survival outcomes can be reported as a percentage of survival at a particular time point, for example, one-year or five-year survival rates, median survival, survival curves, or hazard ratios. Each of these provides different information, and discussion of prognosis may require all of these factors to be discussed in an easily comprehensible fashion that is applicable to the individual.

Guidelines – Informing the Patient	Level of Evidence	Refs
Patients should be provided with adequate information, as this is associated with enhanced patient psychological wellbeing.	III–3	2
Clinicians should follow the NHMRC recommended guidelines on the breaking of bad news, providing information about treatments and the discussion of prognosis.	IV	I

4.2 PREVALENCE OF ANXIETY, DEPRESSION AND DISTRESS

Studies screening patients with lung cancer for evidence of psychological distress have reported rates between 15%[14] and 25%[15]. As the disease becomes more advanced, these rates climb as high as 69%[16]. Studies specifically seeking to identify anxiety disorders have recorded rates between 13% and 50%[17,18,19], while those delineating depressive disorders have identified rates between 9% and 36%[17,18,20,21,22].

In an important study conducted by the British Medical Research Council Lung Cancer Working Party, depression was identified in 33% of patients (n=322) before treatment and persisted in more than 50% of patients following treatment. Small cell lung cancer patients had a three-fold higher prevalence of depression than NSCLC patients[22].

In an Australian study of patients with advanced cancer in the palliative care setting, up to half of the patients, one third of their spouses and one quarter of their offspring showed evidence of substantial psychological distress warranting specific support[23]. The distress reverberates through the family in this setting, such that both patient- and family- centred models of care need to be utilised.

Predictors of anxiety and depressive disorders in patients with lung cancer include poor performance status[22,24], poorly treated pain[16], female gender[22,25] (especially with early stage disease), living alone, lacking confidants and having a hopeless/helpless coping attitude[25]. Pretreatment physical symptom burden, fatigue and physician-rated performance status were also independent predictors of depression, but histological subtype was not[22].

Meta-analyses to evaluate the efficacy of treatment of anxiety and depressive disorders in patients with cancer have demonstrated the importance of recognition and treatment of these medical problems[2,26,27]. Trials of antidepressants in cancer populations show the same level of efficacy as that seen in the treatment of depression in non-cancer populations[28,29].

Guideline – Psychosocial Care in Lung Cancer	Level of Evidence	Refs
It is critical to recognise distress, anxiety and depressive disorders in patients with lung cancer as treatment with combined pharmacotherapy (antidepressants) and psychotherapy is efficacious.	I	2,26,27

4.3 QUALITY OF LIFE

Examination of symptoms at presentation and during treatment for lung cancer show the pattern to be virtually the same for patients with SCLC and NSCLC[30]. Prominent symptoms that affect quality of life include disease-related chest symptoms (shortness of breath, cough and pain); constitutional symptoms (fatigue, anorexia); and psychological concerns (insomnia, decreased libido, worry)[18,30]. In addition, prophylactic cranial irradiation is associated with a transient increase in sickness and vomiting[31]. Studies have varied in their conclusion as to the effect of chemotherapy on quality of life. One study in SCLC showed a diminishing of quality of life with continuing chemotherapy for regimens such as cyclophosphamide/vincristine/etoposide (level II evidence), and this burden of treatment needs to be balanced against tumour response[31]. However, several studies comparing chemotherapy with best supportive care in advanced NSCLC have shown maintenance or improvement in measures of quality of life[32,33,34].

The routine use of computerised quality of life screening using typical scales such as the European Organization for Research and Treatment of Cancer (EORTC) QLQ–C30 has not been shown to improve outcome in patient wellbeing or satisfaction with care in patients with lung cancer[35]. This contrasts with screening for depression or distress, which does generate a significant clinical improvement[36].

Guideline – Quality of Life in Lung Cancer	Level of Evidence	Refs
The potential impact of treatment on quality of life in patients with lung cancer should be included in discussions of treatment alternatives.	II	18,30,31, 32,33,34

4.4 COUNSELLING, SUPPORT AND PSYCHOLOGICAL TREATMENTS

A range of psychological therapies is available to assist in enhancing coping and relieving distress in patients with lung cancer. These interventions can be delivered individually or via group or family approaches, and follow well described models of psychotherapy including the supportive-expressive, cognitive-behavioural, interpersonal, existential and psychodynamic schools of psychotherapy. They enhance emotional adjustment (sense of control, self esteem, living with uncertainty, fear of death, complicated grief and depression); improve functional status (activities of daily living, social and role functioning, vocational activities); improve knowledge of lung cancer and its treatment; improve treatment- and disease-related symptoms (for example, nausea, vomiting, pain etc); and increase overall quality of life. Meta-analyses have confirmed the benefits of these psychological treatments in various cancers [2,26,27].

Relaxation-based therapies provide benefits by reducing anxiety, treatment-related phobias such as needle phobia, conditioned nausea and vomiting, and insomnias[2]. Existential distress, which finds expression in fear of the reality or process of dying, essential aloneness, meaninglessness and unrealistic fears about the processes of treatment, can be ameliorated with supportive-expressive or cognitive-behavioural therapies. Furthermore, compliance with medical therapies can be improved. Early referral for specialist support from a clinical psychologist or consultation-liaison psychiatrist is worthwhile when symptoms of distress or high risk for psychiatric morbidity become evident.

Randomised controlled trials of early versus late referral to palliative care services show strong evidence of the benefits of early referral in reducing time spent in hospital, enhancing symptom control, increasing family satisfaction and permitting death to occur in the desired location[37,38,39]. Early referral to community-based domiciliary palliative care services, where available, may have several benefits and enhance quality of life[40].

Guideline – Psychosocial and Supportive Services in Quality of Life in Cancer	Level of Evidence	Refs
Psychological interventions and early referral to psycho-oncology and palliative care services improves quality of life in patients with cancer.	I II	2,26,27 38,39

SOCIAL SUPPORT

A number of people involved in the patient's care may be involved in providing support in either a formal or informal manner. These can include family, friends, doctors, nurses, and other health care professionals, and together form the treatment team. Co-ordination and continuity of care ensure high quality treatment for patients with lung cancer. The choice of the person to co-ordinate this care should be made by the patient in conjunction with their general practitioner and specialists. This co-ordinator need not necessarily be a health professional.

Assistance with transport, care of children or other family members, home support, respite care and volunteer assistance are some of the many means of social support. State and Territory Cancer Councils provide support through a telephone help line (the national telephone contact number for all such services is 13 11 20). Professional guidance or the support of volunteers is available through such services, together with information about local community self-help groups and related services. Regional Cancer Councils offer a range of educational pamphlets to assist patients and their families.

In summary, the social support needs for patients with lung cancer and their families include:

- access to cancer support services and community self-help groups
- information about community social support resources
- assistance with transport, child care, home help
- guidance about financial and disability support.

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5. NON-SMALL CELL LUNG CANCER

5.1 Management of non-small cell lung cancer by stage

5.2 Surgery

Surgical resection for early stage disease (clinical Stages I and II)

Extent of pulmonary resection

Nodal assessment

5.3 Radiotherapy

Radiotherapy in the treatment of locoregional non-small cell lung cancer

- Dose of radiotherapy
- Duration of radiotherapy
- Radiotherapy versus radiotherapy plus chemotherapy
- Chemotherapy versus radiotherapy with or without chemotherapy
- Timing of chemotherapy/radiotherapy regimens
- Frequency of chemotherapy
- Cisplatin or carboplatin

Radiotherapy or surgery for Stage III disease

Postoperative radiotherapy

Complications of thoracic radiotherapy

5.4 Chemotherapy and adjuvant or neo-adjuvant treatment of locoregional non-small cell lung cancer

Surgery and adjuvant chemotherapy

Surgery and neo-adjuvant chemotherapy

5.5 Chemotherapy in advanced/metastatic non-small cell lung cancer

General aspects

The role of systemic chemotherapy in advanced non-small cell lung cancer

Appropriate chemotherapy for treating advanced non-small cell lung cancer

- Single agent versus combination chemotherapy

Optimal combination chemotherapy for advanced non-small cell lung cancer

- 'New' versus 'old' combinations with platinum
- Cisplatin versus carboplatin trials
- Trials comparing 'new' drug plus platinum combinations
- Non-platinum new drug combinations

Appropriate dose and duration of chemotherapy

The role of second-line chemotherapy and other agents in advanced non-small cell lung cancer

Biological agents

5.1 MANAGEMENT OF NON-SMALL CELL LUNG CANCER BY STAGE

The optimal treatment for lung cancer is surgery. This approach implies that the tumour is at an early stage and that the patient is suitable for optimal regimen. When the disease is more advanced and technically unresectable, or the patient is not fit for surgery radiotherapy, chemotherapy or palliation are appropriate. Table 1–5 provides pathways for care.

Table 1–5 Management of non-small cell lung cancer stage by stage

	Optimal regimen	If patient is not suitable for optimal regimen, treat depending on symptoms and performance status
Stages I & II	Surgical resection	Radical radiotherapy +/- chemotherapy (good performance status) **or** Palliative management (poor performance status) **or** Observation if not symptomatic
Stage IIIA	Induction chemotherapy ➔ Surgical resection ➔ +/- Mediastinal radiotherapy **or** Radical combination chemoradiotherapy	Palliative radiotherapy or chemotherapy **or** Observation if not symptomatic
Stage IIIB	Radical combination chemoradiotherapy	
Stage IV	Chemotherapy **and** Palliative radiotherapy for specific sites of disease (brain, bone pain). Some patients with solitary brain metastases may be suitable for surgical excision	Palliative radiotherapy **or** Supportive care alone

5.2 SURGERY

SURGICAL RESECTION FOR EARLY STAGE DISEASE (CLINICAL STAGES I & II)

Surgical resection has been shown to result in the best five-year disease-free survival rates compared to any other form of treatment for NSCLC. Since the first successful pneumonectomy for NSCLC by Dr Evarts Graham in St Louis in 1933[1], there have been refinements in patient selection, operative techniques and perioperative management which have translated into better survival with reduced postoperative morbidity and mortality.

In looking at historical series of early stage lung cancer survival, it must be remembered that there has been a great variation in the degree of characterisation of metastases and node staging from the techniques used for the evaluation (including CT scanning, PET scanning, routine or selective mediastinoscopy, node sampling or node dissection at operation) as well as the difficulties of naming mediastinal and hilar node disease according to whichever node map was utilised. A recommendation for node classification was revised in 1997[2] and this is currently used in Australia for description of node locations both anatomically and pathologically.

Lung cancer survival following surgical resection was reviewed by Rubins[3] comparing those patients treated between 1947–69 with those treated between 1981–94. This demonstrated that stage for stage the survival over the 47-year period had not altered but the operative mortality had reduced markedly.

Surgery outperforms radiation therapy in the treatment of early stage NSCLC in those patients fit enough to tolerate the required resection. Morrison[4] reported a randomised study comparing radical radiation employing 45Gy in four weeks for early stage disease versus surgical resection. At four years there was a reported 7% survival in the radiation group compared to 23% in the surgical group. Gauden[5] reported the largest retrospective study of radiation for early stage lung cancer demonstrating a five year recurrence-free survival of 23% with the median survival being 19.5 months, significantly less than that reported in comparable surgical series for non-small cell lung cancer.

The Japanese Lung Cancer Screening Research Group[6] studied 69 patients with Stage 1 lung cancer treated non-surgically with either chemotherapy or radiotherapy and found the five-year survival to be 14.3% in screen-detected asymptomatic patients and 3.7% for symptomatic patients. This study emphasised the poor prognosis for Stage I NSCLC patients treated without surgical resection.

Many reviews have been published supporting surgery as the preferred form of treatment for early stage non-small cell lung cancer[7,8,9,10,11]. The overall reported survival for patients with pathological Stage I and II disease is as follows:

Table 2–5 Survival for patients with stage I and 2 non-small cell lung cancer[12]

Pathological stage	Five-year survival (range)		
Stage I	T1 N0	76.0%	(68–83%)
	T2 N0	59.5%	(54–65%)
Stage II	T1 N1	51.9%	(40–63%)
	T2 N1	40.3%	(39–45%)
	T3 N0	38.0%	(25–55%)

Guideline – Non-small Cell Lung Cancer – Surgical Resection	Level of Evidence	Refs
Surgical resection is recommended for early stage non-small cell lung cancer, as this gives the best results of any form of treatment.	II	4

EXTENT OF PULMONARY RESECTION

The extent of pulmonary resection required to yield the optimal survival rates has been reviewed since the first successful pneumonectomy in 1933. Pneumonectomy was initially thought necessary for potential cure but survival data reported in the 1950s indicated that lobectomy was equally effective provided both macroscopic and microscopic clearance of tumour was achieved. Lobectomy was associated with lower operative and long-term mortality and morbidity compared with pneumonectomy.

Lobectomy with mediastinal lymph node dissection is now the gold standard for surgical resection of NSCLC. Pneumonectomy is appropriately reserved for those patients with centrally placed primary tumours crossing the interlobar fissure, involving the main stem bronchi or main pulmonary arteries or in the presence of malignant hilar nodal disease in Stage II NSCLC. For patients with direct invasion of structures adjacent to the lung (T3: parietal pleura, chest wall, pericardium, diaphragm) en bloc resection of lung and involved extra pulmonary structures is associated with five-year survival in excess of 50% in those In whom complete microscopic resection is achieved and the nodal status is N0[13,14].

As with malignancies elsewhere in the body, thoracic surgeons have assessed the role of lesser resections, namely pulmonary segmentectomy or wedge resections, for early stage NSCLC. In a retrospective review Warren and Faber[15] recorded 173 patients with Stage I NSCLC who had undergone either lobectomy or segmental resection. The five-year survival was similar, but there was a significant increase of locoregional recurrence in the segmental resection group (23%) compared to those undergoing lobectomy (5%).

The Lung Cancer Study Group[16] in a prospective, multi-institutional randomised trial compared lobectomy with minimal resection, most commonly segmentectomy. All patients were assessed as fit for lobectomy, and randomised in the operating theatre after frozen section confirmed T1 N0 staging with hilar and mediastinal lymph node sampling. Two hundred and forty seven patients were randomised. In those patients randomised to limited resection there was a significantly increased local recurrence rate, as well as an increased mortality rate related to their lung cancer. The study concluded that "because of the higher death rate and a locoregional recurrence rate associated with limited resection (either segmentectomy or wedge resection), lobectomy still must be the surgical procedure of choice for patients with peripheral T1 N0 NSCLC" [16].

Ichinose[17] studied the correlation of tumour size with lymphatic invasion in resected peripheral Stage I NSCLC and found that as the tumour increased in size, the chance of lymphatic invasion increased from 25% in tumours less than 1cm in diameter to 57% in tumours greater than 3.1cm in diameter. This study emphasised the benefit of lobectomy over lesser resections in Stage I NSCLC.

Furthermore, limited resections are not appropriate for patients with Stage I NSCLC who have adequate pulmonary function for lobectomy. The operative approach for lobectomy has traditionally been via a thoracotomy. Recently video-assisted thoracoscopic techniques (VATS) have been utilised successfully for pulmonary resections including regional lymph node assessment. Sugi[18] studied 100 consecutive patients with clinical Stage IA (T1 N0) NSCLC. Forty-eight patients underwent VATS lobectomy and 52 patients open lobectomy; lymph node dissection was performed in both groups. There were no differences in local recurrence rates (6%) or five-year survival (90% VATS, 85% open) between the two groups. Further studies are required to provide definitive evidence on the relative effectiveness and safety of lobectomy via VATS as compared with open thoracotomy.

Guideline – Non-small Cell Lung Cancer – Lobectomy	Level of Evidence	Refs
Lobectomy is preferred to limited resection in patients with operable T1 N0 NSCLC.	II	16

NODAL ASSESSMENT

Intra-operative and subsequent pathological regional node examination, as with most malignancies, is important in the management of NSCLC. There has been controversy regarding the extent of lymph dissection necessary for optimal results.

Asamura[19] demonstrated that if extensive lymph node sampling is performed, 25% of patients are found to have unsuspected positive nodes (N1 10%, N2 15%). In patients with positive mediastinal nodes 25% had no hilar node involvement. In Asamura's series, Stage I patients had a five-year survival of 92% and a ten-year survival of 87%.

However, the study could not definitively relate the increased survival identified in these Stage I patients as being due to the lymph node resection, as opposed to simply more accurately identifying those patients that were truly Stage I disease.

There has also been debate over whether mediastinal lymphadenectomy has a therapeutic advantage for resected lung cancer. Izbicki et al[20] randomised 182 patients with NSCLC to either standard mediastinal lymphadenectomy (removal of lymph nodes suspected of being involved in the hilar or mediastinal regions) or en bloc radical mediastinal lymphadenectomy (as described by Naruke et al[21]), where all tissue containing mediastinal lymph nodes is removed and en bloc skeletonising of the mediastinum is performed. When matched to T and N status, no difference in survival, site or recurrence was shown. Not surprisingly, staging was more detailed in the radical lymph node dissection group.

A prospective randomised study by Sugi[22] studied 115 patients with peripheral NSCLC less than 2cm in diameter. Patients were randomly assigned to lobectomy with lymph node sampling or lobectomy with radical systematic lymph node dissection. There was no difference in the detection of N1 or N2 positive nodes, no difference in either the local, distant or recurrence rates or in the five-year survival between the two groups (84% for node sampling group and 81% in the node dissection group).

Guideline – Non-small Cell Lung Cancer – Regional Lymph Node Assessment	Level of Evidence	Refs
Regional lymph node assessment should be performed with all lung resections for NSCLC. Radical mediastinal lymph node dissection whilst more accurately staging the patient provides no significant survival advantage over appropriate mediastinal lymph node sampling.	II	19,20,22

5.3 RADIOTHERAPY

RADIOTHERAPY IN THE TREATMENT OF LOCOREGIONAL NSCLC

It has been known for many years that ionizing radiation is capable of killing lung cancer cells and reducing tumour size. In 1932, Pancoast described responses of tumours treated with radiotherapy, but acknowledged that the results "for the most part, have been discouraging"[23]. In 1955, Bromley and Szur were able to confirm Pancoast's original observations through histopathologic examination of 66 lung cancers that were irradiated before resection. Although 17% of the cancers were of the oat cell variety, no tumour was found in 29 of 62 (46.7%) specimens examined[24]. These findings led to uncertainty about the relative values of surgical resection and radiotherapy in the management of operable lung cancer, which was subsequently resolved by a randomised trial conducted at the Hammersmith Hospital. This study showed a statistically significant survival benefit for patients randomised to have radical surgery compared with patients randomised to have radiotherapy (45Gy of megavoltage irradiation), particularly for the subgroup with squamous cell carcinoma[4]. The Hammersmith trial has had a profound influence on subsequent practice such that surgery came to be, and is still regarded as, the treatment of choice for fit patients with resectable lung cancer.

Subsequent studies were designed to examine the value of radiotherapy in the management of patients with inoperable NSCLC, in particular, to determine whether the locoregional cytotoxic effects of radiotherapy translate into a survival advantage compared with placebo or a policy of observation[25,26,27]. Three randomised trials designed to test this hypothesis have been published. One large North American study conducted by the Veterans Administration Lung Cancer Study Group (VALCSG), involving 800 patients, revealed a small but statistically significant advantage for patients with pathologically proven lung cancer confined to the chest who were randomised to radiotherapy compared with placebo[25]. Patients with SCLC were included in this study, but subset analysis indicated that the survival advantage was essentially confined to patients with non-small cell histology/cytology. Two smaller European studies, which included radiotherapy and observation as two of the treatment arms, failed to reveal a survival advantage associated with the use of immediate radiotherapy[26,27]. Not only were these studies smaller than the VALCSG study (249 and 117 patients respectively), and less likely to detect a difference between treatment policies, one study (unlike the VALCSG study), included patients without pathological confirmation of the diagnosis[25], and the other closed prematurely because of poor accrual[26].

Guideline – Non-small Cell Lung Cancer – Radiotherapy	Level of Evidence	Refs
In patients with inoperable NSCLC and who have no evidence of distant metastases, radiotherapy is recommended to locoregional disease because it may be associated with a survival advantage compared with placebo.	II	25

DOSE OF RADIOTHERAPY

The influence of radiotherapy dose on survival in patients with good performance status who have locoregional inoperable NSCLC has been investigated in four randomised trials[28,29,30,31]. A dose of 60Gy given over six weeks was shown to be associated with an improved response rate, but not survival, compared with lower doses in a study of the Radiation Therapy Oncology Group (RTOG)[28]. Importantly, the higher dose did not appear to be associated with increased toxicity. Similarly, no improvement in survival was observed when doses of 50Gy versus 42Gy[29] and 50Gy versus 40Gy[30] were compared. A British study showed a small but statistically significant survival benefit for 39Gy versus 17Gy[31]. A comparison of hyperfractionated radiotherapy (69.6Gy given as 1.2Gy fractions, twice a day) revealed no advantage compared with 60Gy given by conventional fractionation, and that the hyperfractionated schedule was significantly inferior to combined modality treatment with chemotherapy and radiotherapy[32].

Guideline – Non-small Cell Lung Cancer – Radiotherapy Dose	Level of Evidence	Refs
In patients with locoregional inoperable NSCLC and with good performance status, higher doses of radiotherapy are associated with better response and possibly survival. Doses in the vicinity of 60Gy in six weeks are recommended because they are safe and give the highest response rates.	II	28,31

DURATION OF RADIOTHERAPY

It has recently been recognised that prolonging the time over which some epithelial cancers are treated with radiotherapy reduces the probability of local control, most likely by allowing accelerated repopulation of surviving clonogens. To minimise the chance of this occurring, treatment schedules that reduce overall treatment time (accelerated radiotherapy) have been designed and tested. The best known is the CHART (continuous hyperfractionated accelerated radiotherapy) regimen, in which

36 treatments are given in a 12 day period, with six hour intervals between treatments and without weekend interruption. The CHART schedule was shown to be superior to conventionally fractionated radiotherapy in a large multicentre trial, with a 22% reduction in relative risk of death across all patients and a 30% reduction in risk of death for patients with squamous cell carcinoma[33]. This trial included patients with Stage I and II disease, for whom a similar reduction in risk was observed as for patients with more advanced disease. The better survival was due predominantly to improved local control, thus providing proof of the principle that radiotherapy can increase survival in selected patients with NSCLC.

The combination of chemotherapy and radiotherapy is also associated with a survival advantage (see following section). Only one study has directly compared accelerated radiotherapy with combined chemotherapy and radiotherapy. This was a small study with less power than the CHART study to detect a survival advantage, and there was no clear benefit for any of the treatment arms[34]. Thus, it remains unclear whether the survival advantage associated with CHART is of a greater magnitude than that achievable with combined chemotherapy and radiotherapy. As the main drawback associated with the CHART regimen is the timing of much of the treatment outside normal working hours, its use is unlikely to be widely adopted unless it can be shown to have significant advantages over combined chemotherapy and radiotherapy.

RADIOTHERAPY VERSUS RADIOTHERAPY PLUS CHEMOTHERAPY

Using survival as the endpoint, two meta-analyses have established the superiority of combined cisplatin-based chemotherapy and radical radiotherapy over radical radiotherapy alone[35,36]. No survival advantage was observed if the chemotherapy did not contain cisplatin. The magnitude of the effect was similar for patients with Stage I or II disease as well as for those with Stage III disease. The benefit was most evident in patients with good performance status. A survival advantage was also observed in patients with poor performance status but this was not statistically significant.

Guideline – Non-small Cell Lung Cancer – Radiotherapy and Chemotherapy	Level of Evidence	Refs
The combination of cisplatin-based chemotherapy and radical radiotherapy in patients with good performance status is associated with a small but significant survival advantage compared with radiotherapy alone in NSCLC.	I	35,36

The combination of cisplatin and radical radiotherapy was associated with a 13% reduction in risk of death, translating into an absolute survival benefit of 4% at two years and 2% at five years.

CHEMOTHERAPY VERSUS RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

There are a number of studies in which radiotherapy and chemotherapy have been compared directly, but in none of these has a survival advantage been demonstrated for one treatment modality over the other[26,37,38,39].

When the combination of radiotherapy and chemotherapy was compared with chemotherapy alone, in a small Japanese study of patients with Stage III disease who responded to initial cisplatin-based chemotherapy, there was a significant survival advantage for patients having the combined treatment[40]. However, in a larger European study of similar design (patients without evidence of distant metastases who had responded to chemotherapy were randomised to further chemotherapy, or to radiotherapy), the addition of radiotherapy to chemotherapy did not significantly influence survival compared with chemotherapy alone, although it did result in significantly better local control[41].

TIMING OF CHEMOTHERAPY/RADIOTHERAPY REGIMENS

In a meta-analysis, all but one of eleven cisplatin trials had employed sequential chemotherapy followed by radiotherapy[35]. Seven comparisons of concurrent cisplatin/radiotherapy and six comparisons of sequential treatment were found to be associated with similar reductions in risk of death in a later meta-analysis[36]. Two recent studies published since the meta-analyses comparing concomitant chemotherapy and radiotherapy with sequential chemotherapy followed by radiotherapy have revealed a survival advantage in favour of concurrent treatment[42,43].

Guideline – Non-small Cell Lung Cancer – Timing of Radiotherapy and Cisplatin Therapy	Level of Evidence	Refs
Concomitant cisplatin and radiotherapy are associated with a better survival than if the two treatments are given sequentially.	II	42,43

FREQUENCY OF CHEMOTHERAPY

The original European Organization for Research and Treatment of Cancer (EORTC) study, which demonstrated a survival advantage for the concomitant daily administration of cisplatin compared with radical radiotherapy alone, had a third arm in which patients were randomised to have weekly cisplatin[44]. The survival in this arm was intermediate between the other two arms, but was not significantly different from either.

CISPLATIN OR CARBOPLATIN

Both cisplatin and carboplatin have been shown to potentiate radiation-induced cytotoxicity in human lung cancer cell lines in preclinical studies[45]. The effects of carboplatin are similar to those of cisplatin, but of a slightly lower magnitude[26,45,46]. Carboplatin, however, has less neurological, renal and gastrointestinal toxicity than cisplatin. The combination of radical radiotherapy and concomitant carboplatin has been tested against radiotherapy alone, but not against cisplatin and radical radiotherapy. Two studies have shown a survival advantage for the combination of carboplatin and hyperfractionated radiotherapy[47,48]. Three other studies were inconclusive, showing no clear benefit for the addition of concomitant carboplatin to radiotherapy[34,49,50].

RADIOTHERAPY OR SURGERY FOR STAGE III DISEASE

Locally advanced disease characterised by mediastinal lymph node involvement (N2) is usually treated by radiotherapy. Recently there has been increasing interest in the use of surgery in patients with this disease stage, particularly with the demonstration of a survival advantage in two small randomised trials of chemotherapy followed by surgical resection (with and without postoperative radiotherapy) compared with locoregional treatment alone[51,52]. However, in two small trials, the same strategy of preoperative chemotherapy and surgery was compared with radiotherapy[53] and with chemotherapy followed by radiotherapy[54], and there was no evidence of a survival advantage for either approach.

POSTOPERATIVE RADIOTHERAPY

The role of postoperative radiotherapy in patients who have had complete resection of NSCLC has recently been evaluated by meta-analysis[55]. This revealed that in patients with Stage I or II disease, postoperative radiotherapy was detrimental to survival, compared with patients randomised to surgery alone. In patients with Stage III disease the effect of radiotherapy on survival was inconclusive. However, radiotherapy did appear to be associated with a reduction in local recurrence. It is possible that if smaller volumes of normal lung are irradiated using more modern radiotherapy techniques, the improvement in local control might result in a survival advantage. Postoperative radiotherapy using these techniques in patients with Stage III disease warrants further investigation.

Guideline – Non-small Cell Lung Cancer – When to Avoid Radiotherapy	Level of Evidence	Refs
Postoperative radiotherapy in patients with completely resected Stage I or II NSCLC is not recommended because of its detrimental effect on survival.	I	55

COMPLICATIONS OF THORACIC RADIOTHERAPY

Acute side effects of thoracic radiotherapy include anorexia, fatigue and oesophagitis. Oesophagitis is more severe and prolonged in patients treated with accelerated radiotherapy[34]. Delayed side effects include pneumonitis and lung fibrosis. The risk of pneumonitis increases with dose and the volume of lung irradiated. The magnitude of these two risk factors can be expressed as a single quantity, either as the mean lung dose[56], or as the percentage of lung receiving a specified minimum dose derived from dose-volume histogram analysis[57], to predict the probability of a patient developing serious pneumonitis. Much more information correlating risk of pneumonitis with the mean lung dose or the V_{20} (volume of lung receiving 20Gy or more) is required, however, in one single institution series, fatal pneumonitis was not observed if the V_{20} was less than 32%[57].

Spinal cord injury is a potential complication of thoracic radiotherapy, but rarely seen if the dose is under 50Gy using conventional 2Gy fractions. Schultheiss has estimated the risks to be 0.2% after 45Gy and 1–5% at five years after 60Gy with conventional fractionation[58].

5.4 CHEMOTHERAPY AND ADJUVANT OR NEO-ADJUVANT TREATMENT OF LOCOREGIONAL NON-SMALL CELL LUNG CANCER

SURGERY AND ADJUVANT CHEMOTHERAPY

The strongest evidence regarding the role of postsurgical adjuvant chemotherapy is derived from the meta-analysis of randomised trials comparing adjuvant chemotherapy to no adjuvant chemotherapy carried out by the Non-Small Cell Lung Cancer Collaborative Group.

Patients who received adjuvant chemotherapy in five trials using non-platinum based regimens had worse survival. There was a 15% increase in the relative risk of death (p=0.005) with an absolute reduction in survival of 4% at two years and 5% at five years. These regimens are alkylating agent-based and are no longer used in clinical practice.

In eight trials investigating platinum-based regimens, there was a 13% decrease in the relative risk of death with adjuvant chemotherapy (p=0.08). Absolute survival was improved by 3% at two years and 5% at five years. These differences were not statistically significant.

The meta-analysis also addressed the question of the role of combined chemotherapy and radiotherapy given in the adjuvant setting. Four trials compared adjuvant chemoradiation versus adjuvant irradiation alone. For cisplatin-based combination chemotherapy there was a 6% decrease in the relative risk of death (p=0.46). Absolute survival was increased with chemotherapy by 2% at two years and 2% at five years. These differences were not statistically significant[35].

Guideline – Non-small Cell Lung Cancer – Adjuvant Therapy	Level of Evidence	Refs
The administration of adjuvant platinum-based chemotherapy is not recommended following surgery because it has not been definitively shown to significantly improve survival.	I	35

SURGERY AND NEO-ADJUVANT CHEMOTHERAPY

Under this section, studies were included where patients planned for surgical resection were randomised to receive chemotherapy or no chemotherapy prior to surgery (with or without radiotherapy). A list of these trials is given in Table 3–5. Evidence for the benefit of neo-adjuvant cisplatin-based chemotherapy comes from the two fully published trials[51,52], for which long-term follow-up has recently been published[59,60]. Four other studies using cisplatin-based chemotherapy[61,62,63,64] and one using single agent docetaxel[65,66] were inconclusive.

In the study from Roth et al, 60 patients with Stage IIIA NSCLC were randomised to surgery alone (32 patients), or surgery preceded by three cycles of cisplatin, etoposide and cyclophosphamide (28 patients)[52,59]. Postoperative radiotherapy was given to patients with unresectable disease, or if the resection had been incomplete. The trial was stopped after a single unplanned interim analysis due to significantly improved median survival in the chemotherapy arm, 64 months versus 11 months (p<0.008).

An update of this study, with median follow-up of 82 months, has recently been reported[59]. Median survival was 21 months in the perioperative chemotherapy arm and 14 months in the surgery-alone arm (p=0.056 log rank test, p=0.048 Breslow-Gehan-Wilcoxon test). The overall three- and five-year survival was 43% and 36% respectively for the chemotherapy arm, and 19% and 15% for the surgery-alone arm.

In the second fully reported study, from Rosell et al, 60 patients with Stage IIIA NSCLC were randomised to surgery, or surgery preceded by three cycles of mitomycin C, ifosfamide and cisplatin[51,60]. All patients received thoracic irradiation after surgery. Interim analyses were planned for 12, 18 and 24 months from the start of the study. Accrual was stopped after 24 months when a significant median survival difference in favour of the chemotherapy arm became apparent, 20 months versus 5 months, ($p<0.001$). A recent seven-year update of the results of this study showed that median survival was 22 months for the chemotherapy group and 10 months for the surgery-alone group ($p=0.005$ log rank test)[60]. Three- and five-year survival rates were 20% and 17% respectively for the chemotherapy arm, compared with 5% and 0% for the surgery-alone arm.

Further studies are required to establish the categories of Stage IIIA patients for whom the neo-adjuvant chemotherapy followed by surgery is appropriate, and to clarify its efficacy relative to non-surgical interventions.

Guideline – Lung Cancer – Neo-adjuvant Therapy	Level of Evidence	Refs
For Stage IIIA patients managed surgically, platinum-based combination chemotherapy should be given prior to surgery as it improves survival. Neo-adjuvant chemotherapy may be beneficial in earlier stage disease, but the evidence is currently insufficient to support routine use (see Table 3–5).	II	51,52, 59,60

Table 3–5 Trials of surgery with or without preoperative chemotherapy in Stage IIIA non-small cell lung cancer

Author	Stage	No (patients)	Design	Outcomes
Pass 1992 [61]*	Stage III (N2)	27	CT + S + CT vs S + RT	Median survival CT/S 29 months vs S 16 months (p=0.095).
Roth 1994 [52]* Roth 1998 [59]*	Stage IIIA	60	CT + S +/- CT vs S +/- RT (CEP)	Trial stopped at unplanned interim analysis. Median survival superior in CT arm, 21 months vs 14 months (p=0.05). 5-year survival superior in the CT arm, 36% v 15%.
Rosell 1994 [51]* Rosell 1999 [60]*	Stage IIIA	60	CT + S + RT vs S + RT (MIC)	Trial stopped at planned interim analysis. Median survival superior in CT arm, 22 months vs 10 months. (p=0.005), 5-year survival superior in the CT arm, 17% vs 0%.
Depierre 1999 [63]*	Stage IB–IIIA Stage IIIA	373 167	CT + S +/- CT vs S (MIC)	Median survival superior in CT arm, 37 months vs 26 months (p=0.09). On multivariate analysis, relative risk of death for CT arm 0.77 (p=0.05). Perioperative mortality non-significantly increased in CT arm.
Mattson 2000 [66]*	Stage IIIA	274	CT + RT vs RT or CT + S vs S (docetaxel)	Median survival superior in CT arm, 15 months vs 13 months (ns).
Elias 1997 [62]*	Stage IIIA (N2)	47	CT + S + CT + RT vs RT+S+RT (PE)	Median survival CT/S 19 months RT/S 23 months (ns).
Ichinose 2000 [64]*	Stage IIIA (N2)	62	CT + S vs S (PV)	Median survival CT/S 18 months S 16 months (p = 0.6).

* = reference

CT chemotherapy; S surgery; RT radiotherapy; CEP cyclophosphamide, etoposide, cisplatin; MIC mitomycin, ifosfamide, cisplatin; PE cisplatin, etoposide; PV cisplatin vindesine; ns non-significant

5.5 CHEMOTHERAPY IN ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER

GENERAL ASPECTS

Patients with advanced/metastatic NSCLC consist of those patients whose disease is either:

- Stage IV (distant metastases) at the time of diagnosis of NSCLC
- Stage IV (distant metastases) developing after treatment for earlier stage NSCLC
- recurrent local intrathoracic disease after treatment for NSCLC
- unresectable Stage IIIB with disease beyond suitability for radical irradiation (for example, pleural effusion).

There are a group of patients who present with earlier stage NSCLC, but who are not able to receive surgical or radical irradiation because of major comorbidity or other factors. While the management of such patients has elements in common with the management of advanced NSCLC, they are not usually included with advanced NSCLC patients in clinical trials, particularly trials of systemic therapies.

The aim of treatment of advanced NSCLC is palliative. The palliative management of advanced NSCLC may involve treatment by oncologists, respiratory medicine physicians, palliative care physicians, and occasionally other medical specialists. The active participation of the patient's general practitioner is very important. The specific goals of treating advanced NSCLC are to:

- extend the patient's life
- relieve the patient's symptoms
- improve the patient's quality of life.

When evaluating clinical trials, the important endpoints are therefore survival, changes in symptoms, and changes in quality of life. The response rate to a treatment, while often the primary endpoint of phase II trials, is not of comparable interest.

The management of symptoms from metastatic NSCLC is covered elsewhere in these guidelines (refer to Chapters 7 and 8). Some sites of disease (for example, brain metastases with cerebral oedema, vertebral metastases with spinal cord compression) and syndromes (for example, malignant hypercalcaemia) are better palliated with non-chemotherapy treatments (for example, radiation therapy, bisphosphonates). Chemotherapy should not therefore be used as the primary treatment for these problems.

THE ROLE OF SYSTEMIC CHEMOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER

Three meta-analyses have been published examining the influence of chemotherapy on survival in advanced/metastatic NSCLC[35,67,68]. The Non-Small Cell Lung Cancer Collaborative Group meta-analysis[35] was of 11 randomised controlled trials involving 1 190 patients randomised to either chemotherapy or no chemotherapy. The other two meta-analyses were smaller (six and seven trials respectively) and all trials analysed by these groups were included in the Non-Small Cell Lung Cancer Collaborative Group meta-analysis. Therefore this analysis, which was based on individual patient data, is the most comprehensive.

Chemotherapy provided a modest but highly statistically significant improvement in survival over supportive care alone[35]. Statistical heterogeneity was apparent concerning the type of chemotherapy, such that a detrimental effect was observed for the two trials that used long-term administration of alkylating agent chemotherapy, no effect was seen in one trial that used vinca alkaloid/etoposide chemotherapy, and significant benefit was seen for the seven trials that used cisplatin-based chemotherapy. In the cisplatin chemotherapy trials (totalling 778 patients), the hazard ratio for death at one year was 0.73 (CI 0.63–0.85), corresponding to an absolute improvement in one-year survival from 16% to 26% and an improvement in median survival from 4.0 months to 5.5 months. For all chemotherapy trials (1190 patients), the hazard ratio for death at one year was 0.84 (CI 0.74–0.95).

This meta-analysis examined the influence of disease extent on the beneficial effect of cisplatin-based chemotherapy, analysing the following: metastatic versus non-metastatic, histological subtype (squamous versus adenocarcinoma versus other), performance status ('good' versus 'poor'), age, and sex. All subgroups were found to derive benefit from treatment[35].

Data on relief of symptoms and changes in quality of life were not uniformly collected in the trials that were combined in these meta-analyses, and no analysis of these endpoints was performed.

Since the publication of the Non-Small Cell Lung Cancer Collaborative Group meta-analysis, six other trials have been reported where patients were randomly allocated to treatment with chemotherapy or to not receive chemotherapy. Cullen et al[69] used a combination of cisplatin, ifosfamide and mitomycin C in a trial of 351 patients with metastatic NSCLC. There was a significant prolongation of median survival (6.7 months versus 4.8 months, p=0.03) with chemotherapy. Quality of life was assessed in a subset of patients only, and showed an improvement over the first six weeks with chemotherapy, whereas it progressively declined in the no-chemotherapy patients. A study from Thailand randomised 287 patients to either cisplatin; ifosfamide and epirubicin chemotherapy; cisplatin/mitomycin C/vinblastine chemotherapy or no chemotherapy. Survival was significantly prolonged in both chemotherapy arms, and quality of life (using modified, translated 'Western' scales) was significantly improved with chemotherapy[70].

The other four trials compared single agent chemotherapy using one of the newer cytotoxic agents introduced in the 1980s and 1990s (hereafter referred to 'new' agents)[71,72,73,74]. These trials are summarised in Table 4–5. Significant beneficial effects were found on survival and/or symptom control and quality of life in all studies. Patients with performance status of greater than 2 (see Appendix 3) or with other major co-existing medical problems were generally excluded from clinical trials.

Many other clinical factors have been shown to be markers of poor prognosis in advanced NSCLC patients[75]. However, there is no evidence that benefit experienced from chemotherapy is confined to particular patient subgroups. In particular, both a meta-analysis and a large randomised trial did not identify extent of metastatic disease, histological subtype, age, or sex as predictors of benefit[35,69]. Only one trial has specifically enrolled only elderly (age ≥70 years) patients[74]. This trial showed significant prolongation of survival with single-agent vinorelbine chemotherapy compared to supportive care.

Table 4–5 Randomised trials of 'new' agents versus supportive care

Study agent	Patients	Survival	Quality of life	Ref
Paclitaxel	157	Significantly improved with paclitaxel	No significant difference	71
Gemcitabine	300	No significant difference	Better QOL and better symptom control with gemcitabine	72
Docetaxel	207	Significantly improved with docetaxel	Better QOL and better symptom control with docetaxel	73
Vinorelbine	191*	Significantly improved with vinorelbine	Better QOL and better symptom control with vinorelbine	74

* trial restricted to patients aged ≥ 70 years. QOL – quality of life

Guidelines – Non-small Cell Lung Cancer – Chemotherapy	Level of Evidence	Refs
Chemotherapy is appropriate treatment for patients with advanced NSCLC who have good performance status (ECOG ≤ 2) and are otherwise medically fit as it has been shown to improve survival.	I	35
Chemotherapy can result in beneficial effects on symptoms and quality of life in patients with advanced NSCLC.	II	69,70

APPROPRIATE CHEMOTHERAPY FOR TREATING ADVANCED NON-SMALL CELL LUNG CANCER

SINGLE AGENT VERSUS COMBINATION CHEMOTHERAPY

The evidence for benefit from cisplatin-based chemotherapy on survival was derived from trials where cisplatin was combined with older drugs including vinca alkaloids (vindesine, vinblastine), etoposide, doxorubicin, cyclophosphamide and mitomycin C[35]. Another meta-analysis (using only published trials, without individual patient data) has examined the effect on response rates, survival and toxicity of combination chemotherapy compared to single-agent chemotherapy[76]. Combination chemotherapy produced a significantly higher response rate, significantly better six- and 12-month survival and higher levels of toxicity. However, benefit on survival was not apparent when only trials that had cisplatin or vinorelbine as the single-agent arm were considered, suggesting that the overall benefit was attributable to older trials where the single-agent arm was ineffective. Further studies are required to better define the role of single-agent therapy with the 'new' agents compared to combination chemotherapy. This is particularly important for patients with performance status 2, who may not tolerate combination chemotherapy, as well as for better performance status patients.

Several more recent trials have compared the combination of a 'new' drug plus cisplatin with cisplatin alone. These are summarised in Table 5–5. All trials except one have shown significantly improved survival with the combination.

Table 5–5 Randomised trials of 'new' agents plus cisplatin versus cisplatin

New agent	Patients	Survival	Quality of life	Ref
Paclitaxel	414	No significant difference	No significant difference	77
Vinorelbine	432	Significant survival advantage with combination	Not assessed	78
Gemcitabine	552	Significant survival advantage with combination	No significant difference	79
Tirapazamine	446	Significant survival advantage with combination	No significant difference	80

One phase III trial of 169 patients has compared single agent gemcitabine to the combination of cisplatin and vindesine. Survival and control of symptoms were equivalent, but quality of life improved in more patients in the gemcitabine arm[81,82]. Two smaller trials have compared single agent gemcitabine to the combination of cisplatin and etoposide[83,84]. With short follow-up, both trials reported no difference in response rate or survival. As expected, in all these trials, the cisplatin arms had more severe toxicity than single-agent therapy. None of these trials is large enough to be adequately powered to exclude inferior survival with gemcitabine compared to the combination therapy.

Guidelines – Non-small Cell Lung Cancer – Combination Chemotherapy	Level of Evidence	Refs
Combination chemotherapy is preferable to single agent therapy in patients with advanced NSCLC.	I	76
For patients where combination chemotherapy is contraindicated, single agent therapy with one of the 'new' agents (either a taxane, gemcitabine or vinorelbine) is appropriate.	II	83,84

OPTIMAL COMBINATION CHEMOTHERAPY FOR ADVANCED NSCLC

'NEW' VERSUS 'OLD' COMBINATIONS WITH PLATINUM

A series of trials have compared 'old' platinum combinations (for example, cisplatin plus vinca alkaloid, cisplatin plus etoposide/teniposide) to 'new' platinum combinations. The 'new' combinations tested include cisplatin combined with paclitaxel[85,86], vinorelbine[87], gemcitabine[88,89], tirapazamine[90] and irinotecan[91]. In some studies there was a modest survival benefit for the new regimen[85,87] and in others improved quality of life[86]. In the remainder, survival and quality of life outcomes were similar in both arms.

CISPLATIN VERSUS CARBOPLATIN TRIALS

Combination chemotherapy regimens using either cisplatin or cisplatin replaced by carboplatin have been directly compared in three phase III trials[92,93,94]. There was no consistent evidence of the superiority of one drug over the other. Emesis and renal toxicity were greater with cisplatin whereas haematological toxicity was greater with carboplatin.

TRIALS COMPARING 'NEW' DRUG PLUS PLATINUM COMBINATIONS

Many trials have been performed in the last five years comparing various 'new' regimens. The large majority of these have been published only in abstract form. The results of some of the largest trials are summarised in Table 6–5.

The largest trial[95] was conducted by the Eastern Cooperative Oncology Group (ECOG) in the US. Over 1 200 patients were randomised to the control arm of paclitaxel over 24 hours plus cisplatin[85] or one of three other regimens. Response rate and overall survival times were not significantly higher in any of the three experimental arms. A marginal but statistically significant benefit in time to progression was found in the cisplatin/gemcitabine arm, however, the chemotherapy in this arm was administered every four weeks, rather than every three weeks as in the control arm, making assessment of this endpoint difficult. Toxicity was variable, but less acute emesis and febrile neutropenia occurred in the carboplatin/paclitaxel arm. The inconvenience of the 24-hour paclitaxel infusion makes this regimen less suited to the palliative setting. While no significant disadvantage occurred with cisplatin/docetaxel, the activity of docetaxel in second-line therapy (see below) indicates alternative drugs may be preferable for first-line therapy.

The above ECOG trial was originally intended to enrol patients with performance status 0,1 or 2 but a high rate of toxicity resulted in termination of accrual of performance status 2 patients. Most other trials in Table 6–5 have been restricted to performance status 0 or 1 patients.

Two trials have evaluated the addition of a third 'new' agent to a new drug plus platinum combination[96,97]. In one trial[96] the initial report has shown significant benefit to the triplet combination. Other trials examining various triplet combinations are being conducted.

Table 6–5 Randomised trials of 'new' agents

Design	Patients	Outcome	Ref
cisplatin/paclitaxel vs cisplatin/gemcitabine vs cisplatin/docetaxel vs carboplatin/paclitaxel	1207	Survival and response rates equivalent. Longer time to progression with cisplatin/gemcitabine. Less nausea and febrile neutropenia with carboplatin/paclitaxel.	95
cisplatin/gemcitabine vs cisplatin/gemcitabine/paclitaxel vs cisplatin/gemcitabine/vinorelbine	371	Triplet arms had superior survival and longer time to worsening symptoms.	96
paclitaxel/carboplatin vs paclitaxel/gemcitabine	329	Equivalent response rate, survival and toxicity.	98
paclitaxel/carboplatin vs cisplatin/vinorelbine	444	Equivalent survival and QOL. Less haematological toxicity and emesis with carboplatin/paclitaxel.	99
docetaxel/cisplatin vs docetaxel/gemcitabine	414	Equivalent response rate and survival. More diarrhoea with docetaxel/cisplatin. Both arms received G-CSF support.	100
gemcitabine/cisplatin vs vinorelbine/cisplatin vs cisplatin/vinorelbine/gemcitabine	180	Cisplatin/vinorelbine closed at interim analysis because of worse survival. Accrual continues to other arms.	97
gemcitabine/vinorelbine vs vinorelbine	120*	Closed at interim analysis because of survival benefit with combination. Longer time to symptom and QOL deterioration with combination.	101

*Trial restricted to patients aged ≥70 years
QOL = quality of life; G-CSF = granulocyte colony stimulating factors

Other platinum-ased combinations such as carboplatin plus gemcitabine or carboplatin plus vinorelbine have been investigated in phase II trials and have shown some activity, but phase III data to support their use is lacking.

NON-PLATINUM NEW DRUG COMBINATIONS

Two phase III trials have compared the combination of two new drugs with a platinum plus one new drug combination[98,100] (Table 6–5). Neither trial showed any benefit of the non-platinum arm in terms of response rate or survival. Both trials failed to show a marked reduction in toxicity with the omission of platinum.

One trial restricted to elderly patients compared the combination of gemcitabine and vinorelbine to vinorelbine alone[101]. This trial was closed with accrual of only 120 patients because an interim analysis showed a significant benefit with the combination. The results obtained with the vinorelbine alone arm in this trial appear substantially worse than the previous trial performed by this group[74].

Guidelines – Non-small Cell Lung Cancer – Choice of Chemotherapy Agents	Level of Evidence	Refs
At the present time, no one chemotherapy regimen can be recommended over another. Based on currently available trial results, various combinations of a platinum drug plus a 'new' agent are reasonable options for performance status 0 or 1 patients. The use of combinations of three or more drugs, and the use of non-platinum combinations require further investigation before incorporation into standard practice.	II	85,86,87,88
Carboplatin can be used instead of cisplatin in combination chemotherapy.	II	92,93,94

APPROPRIATE DOSE AND DURATION OF CHEMOTHERAPY

The clinical trials evaluating various cytotoxics in NSCLC have used doses derived from phase I and II studies where routine use of colony-stimulating factor support, stem-cell support or use of cytoprotectants such as amifostine was not permitted. Only a small number of trials have specifically addressed cytotoxic doses in NSCLC patients. Two trials evaluating higher does of paclitaxel[85,102] have shown no survival benefit for the higher dose. Increased frequency[103] or dose of cisplatin[104] have not been shown to be more effective than four weekly administration or lower doses (50 mg/m^2) respectively.

In most of the discussed clinical trials in advanced NSCLC, treatment was generally administered for up to six to nine cycles in the absence of disease progression or severe toxicity. The cumulative non-haematological toxicity seen with agents such as platinum, paclitaxel, docetaxel and vinorelbine makes prolonged administration unfeasible. In trials where symptom control has been assessed in detail, improvement with chemotherapy is apparent within two to three cycles, and correlates with response or non-progression on radiological assessments.

Two recent trials have addressed the duration of chemotherapy. One trial[105] compared the administration of three or six cycles of the older cisplatin/vinblastine/mitomycin C combination, and reported that there were no differences in survival or symptom relief between the schedules. A second trial[106] used the more currently accepted combination of carboplatin and paclitaxel. Patients were randomised to receive four cycles or to continue to receive treatment until documented disease progression. No difference in survival was reported, and as expected the continuous arm had an increasing incidence of peripheral neuropathy. Neither of these trials directly randomised only responding patients to continue or cease treatment, although a retrospective analysis of the data from the first trial suggests that stopping therapy is not detrimental to these patients[106].

As only a minority of advanced NSCLC patients will show significant reduction of tumour mass with chemotherapy, it is particularly necessary to take care to avoid continuation of ineffective therapy.

Guidelines – Non-Small Cell Lung Cancer – Chemotherapy Doses and Cycles	Level of Evidence	Refs
There is no indication to use greater than standard doses or dose intensity of chemotherapy in advanced NSCLC.	II	85,102, 103,104
Continuing multi-agent platinum-based chemotherapy beyond three to four cycles does not provide additional survival benefit.	II	105,106
Patients receiving chemotherapy for advanced NSCLC should be evaluated for effectiveness of treatment after two to three cycles. Treatment should be discontinued if no benefit is seen.	IV	106

THE ROLE OF SECOND-LINE CHEMOTHERAPY AND OTHER AGENTS IN ADVANCED NON-SMALL CELL LUNG CANCER

Most studies in which the use of second-line chemotherapy at the time of progression or relapse has been evaluated are phase II trials[107]. These involve small numbers of patients and little information is provided on the performance status and the extent and nature of prior treatment of the patients. The rate of response to treatment is often the major endpoint assessed and the trial designs do not allow for any reliable assessment of patient benefit to be made.

Two randomised phase III studies of docetaxel in patients previously treated with cisplatin-based chemotherapy are available. Both showed a survival advantage: one compared docetaxel with best supportive care[108] and the other compared docetaxel with vinorelbine or cyclophosphamide[109].

BIOLOGICAL AGENTS

The role of biological agents in NSCLC is an emerging area of research. Numerous compounds are in various phases of preclinical and clinical development. A promising group of small molecules are inhibitors of the epidermal growth-factor tyrosine kinase. Early phase studies suggest that symptom improvement can occur with the use of these compounds. However, further research is required before these compounds have an established place in lung cancer management.

Guideline – Non-small Cell Lung Cancer – Second Line Chemotherapy	Level of Evidence	Refs
In selected good performance status patients, second-line chemotherapy with docetaxel may be considered.	II	108,109

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6. SMALL CELL LUNG CANCER

6.1 MANAGEMENT OF SMALL CELL LUNG CANCER BY STAGE

Table 1–6 Management of small cell lung cancer stage by stage

	Optimal management	If patient is not suitable for optimal management
Limited Disease	Platinum based chemotherapy (4–6 cycles) combined with thoracic radiotherapy concomitant with first or second cycle Prophylactic cranial irradiation for complete responders	Palliative chemotherapy +/- radiotherapy
Extensive Disease	Combination chemotherapy (4–6 cycles) Prophylactic cranial irradiation for complete responders	Symptom control

6.2 CHEMOTHERAPY AND SMALL CELL LUNG CANCER

The recognition during the 1970s that SCLC is a systemic disease, best treated with chemotherapy, led to the relegation of radiotherapy to a secondary role in its management. Chemotherapy is associated with high response rates, but most patients subsequently relapse, and the efficacy of available cytotoxic drugs appears to have plateaued. Furthermore, observations in patients treated with chemotherapy alone revealed that the primary site, where the disease was usually bulkiest, and the brain, which is a chemotherapy sanctuary site, were common sites of treatment failure. Multimodality strategies designed to address these problems has resulted in a re-emergence of radiotherapy, particularly in the management of limited disease. As a result, about a quarter of patients with limited disease can now be cured with a combination of chemotherapy and radiotherapy, but the majority of patients who present with extensive disease will nearly all succumb to it.

OCA AND PE

The two most widely used regimens have been vincristine, adriamycin and cyclophosphamide (known variously as OCA, VAC, or CAV) and, more recently, cisplatin with etoposide (PE). Median survival of 12–18 months in limited stage and 7–12 months in extensive stage SCLC have been routinely reported with either of these regimens. An analysis of results through the 1970s and 1980s for the control arms of 21 randomised phase III trials in extensive disease showed a modest improvement in median survival from 7.0 months, for patients enrolled between 1972 and 1981, to 8.9 months for the 1982–90 cohort[1].

Impressive results have been achieved with four cycles of PE in a recent study. Four hundred and nineteen patients with limited stage disease received identical chemotherapy but were randomised to differing schedules of thoracic radiotherapy. Two-year survival was 41% and five-year survival 16% for once daily therapy, while twice daily therapy was better, yielding 47% survival at two years and 26% at five years[2].

A number of studies have compared outcomes with OCA and PE. Larger trials have included a study from the Southeastern Cancer Study Group, where 437 patients with extensive stage disease were randomised to 12 weeks of PE, or 18 weeks of either OCA or OCA/PE alternating. There was no difference in response or survival between the PE and OCA arms[3]. In a South Western Oncology Group (USA) (SWOG) study, 400 limited stage patients were randomised to a platinum-containing arm of alternating PE and OCA, versus etoposide, vincristine, adriamycin and cyclophosphamide. Median survival was 15–16 months and was not different between the arms[4]. In a study from Fukuoka, 288 patients with limited or extensive stage disease were randomised to PE, OCA, or an alternating regimen. Patients also received radiotherapy. Response rates were 78% with PE and 55% with OCA. There was no difference in survival between these two regimens, but there was significantly more toxicity (haematological and neurological) in the OCA arm[5].

Two meta-analyses have looked at randomised trials comparing platinum-containing and non-platinum regimens. The first, from Pujol, included 18 trials, with a total of 4 054 patients. Response rate was higher for cisplatin-containing regimens, with an odds ratio of 1.35 ($p<0.00001$). Survival favoured cisplatin-containing regimens, with six-month survival 68% versus 65% and 12-month survival 29% versus 24%. The odds ratio for survival was 0.87 at six months ($p=0.03$) and 0.80 at 12 months ($p=0.002$). Results were unaltered when considering only trials where both arms included etoposide[6].

The second meta-analysis included 36 trials, and focused on the role of etoposide as well as cisplatin. Only fully published trials were included. Overall survival benefit was shown for regimens containing cisplatin (OR 0.61, $p<0.001$) or etoposide (OR 0.65, $p<0.001$.) Nine trials, involving 1 945 patients, specifically compared a regimen containing both cisplatin and etoposide versus a regimen containing neither drug. The meta-analysis favoured the PE combination (OR 0.57, $p<0.001$)[7].

Neither of the meta-analyses examined individual patient data, however, despite this limitation, there is clear benefit for regimens containing both cisplatin and etoposide. A further consideration for patients undergoing radiotherapy is the toxicity of the chemotherapy regimen in this context. OCA is associated with greater toxicity than PE when combined with radiotherapy. If radiotherapy is to be administered concurrently with chemotherapy then a combination of a platinum agent and etoposide is suggested.

ALTERNATING REGIMENS

In an effort to improve results, alternating or sequential regimens, particularly of OCA and PE, have been used. Results have, for the most part, not shown an advantage for any particular approach. There were no significant differences in outcome in a trial of 437 patients with extensive disease randomised to 12 weeks of PE, 18 weeks of OCA or 18 weeks of alternating OCA/PE[3]. In a phase III SWOG trial, 400 patients with limited stage disease were randomised to alternating PE/OCA or a combination of etoposide with OCA, with chest radiotherapy. There were no significant differences in response rate or survival[4]. In a study from the National Cancer Institute of Canada, 300 patients with limited disease were randomised to three cycles of OCA followed sequentially by three cycles of PE, or alternation of the two regimens. There were no observed differences in patient outcome between the regimens[8]. In a study of 129 patients, following initial therapy with four cycles of PE, responding patients were randomised to no further treatment or to consolidation with OCA. Survival was no different between the arms, but toxicity was increased in the consolidation group[9].

However, some studies have shown improved results with alternating regimens. Two hundred and eighty nine patients with extensive disease were randomised to receive OCA or OCA alternating with PE. Alternating therapy was associated with improved response rate and overall survival[10]. Alternating PE/OCA was also superior to OCA in the trial from Fukuoka, but not significantly superior to PE alone[5]. Positive results in these two trials may be interpreted as superiority of a platinum-containing regimen.

In summary, the evidence for alternating regimens is inconsistent. The superiority of alternating therapy has not been clearly demonstrated.

CARBOPLATIN VERSUS CISPLATIN

Carboplatin has been widely used in Australia to replace cisplatin in the PE regimen[11], although few trials have compared carboplatin and cisplatin regimens. In a study from Greece, patients were randomised to either cisplatin and etoposide, or carboplatin and etoposide. Patients could also receive radiotherapy. One hundred and forty three patients were included, 82 with limited disease. There was no difference in response rate or overall survival between the two arms. However, there was less toxicity (neutropenic sepsis, emesis, nausea and vomiting, neurotoxicity) in the carboplatin arm[12]. Lassen has reported on 484 patients randomised to either cisplatin or carboplatin in combination with teniposide and vincristine. In addition, the regimen was alternated with one of three other regimens. There was no difference in response, survival or toxicity rates between the cisplatin and carboplatin arms[13].

ORAL ETOPOSIDE

Oral etoposide has been investigated as a potential effective, low-toxicity oral regimen for SCLC in randomised trials. Souhami and colleagues randomised 155 patients to six cycles of either oral etoposide (100mg bd x 5d) or alternating PE/OCA. The study was closed early due to toxicity. One-year survival was worse in the oral etoposide arm than the intravenous arm (9.8% versus 19.3% respectively, $p<0.05$), with median survival 4.8 months versus 5.9 months. With the exception of chemotherapy-induced emesis, symptom control and quality of life favoured the intravenous regimen[14]. The UK Medical Research Council Lung Cancer Working Party trial was also stopped after interim analysis. Three hundred and thirty nine patients were randomised to oral etoposide (50mg bd for 10d), or either OCA or PE. Survival was inferior in the oral arm (OR 1.35, $p=0.03$), with median survival 130 days versus 183 days for the intravenous arm. Survival at six months was 35% and 49%, and at 12 months 11% and 13% for the oral and intravenous regimens respectively. The palliative benefits were similar for each of the arms[15]. These data indicate that oral etoposide is inferior treatment to combination intravenous regimens in terms of survival, with no additional quality of life or symptom control benefit.

OTHER REGIMENS

The role of **ifosfamide** has been examined in a phase III study of 162 patients with extensive stage disease. Patients were randomised to receive PE or PE plus ifosfamide. Median survival was longer in the ifosfamide arm, 9.1 months versus 7.3 months, with 12 month survival of 36% versus 27% respectively[16]. A smaller randomised trial of 92 patients including both limited and extensive disease showed no difference in response rates or survival when ifosfamide was added to cisplatin/etoposide[17]. Trial JCOG 9511, investigating irinotecan (CPT-11), has been reported in abstract form only. One hundred and fifty four patients with extensive disease were randomised to receive either cisplatin/etoposide or cisplatin/irinotecan (PI). The trial was stopped at interim analysis. Response rate was 67% with PE and 89% with PI (0=0.013). Median survival was 287 days with PE and 390 days with PI ($p=0.004$)[18]. A confirmatory study is currently being undertaken.

MAINTENANCE THERAPY

A number of trials have examined the role of maintenance therapy in SCLC, generally without improvements in overall survival. Patients with limited or extensive stage disease received ifosfamide, etoposide and an anthracycline (doxorubicin or epirubicin). Responding patients (n=84) were randomised to maintenance etoposide and vindesine for 12 courses, or no further therapy. Progression-free survival was increased but survival was not significantly different[19]. The ECOG 7593 trial has been reported in abstract form only. Patients with extensive stage disease received initially four cycles of cisplatin and etoposide. Those stable or responding were then randomised (n=227) to four additional cycles of topotecan or no further therapy. Progression-free survival was improved but overall survival and 12 month survival was no different[20].

THE OPTIMUM CHEMOTHERAPY REGIMEN

Guidelines – Small Cell Lung Cancer – Platinum as Optimal Chemotherapy	Level of Evidence	Refs
Platinum containing regimens produce superior survival to that seen with other regimens.	I	6,7
For patients with limited disease, when used in conjunction with thoracic irradiation, there is no evidence that any combination is superior to the doublet of cisplatin and etoposide.	I	12,13

APPROPRIATE DURATION OF CHEMOTHERAPY

Studies have compared four to six cycles of chemotherapy versus longer treatment durations. In a study including both limited and extensive stage disease, 265 patients were randomised to six or 12 cycles of chemotherapy. Survival was not different between the arms[21]. Six hundred and ten patients, again of mixed stage, were randomised to receive either four or eight cycles of cyclophosphamide, etoposide, and vincristine. Time to progression was increased in the longer arm, but survival was no different as long as patients in the short arm received further chemotherapy at relapse[22]. Giaccone has reported on 434 patients of mixed stage, randomised to either five or 12 cycles of cyclophosphamide, adriamycin and etoposide. Again, time to progression was increased in the longer treatment arm, but survival was no different. There was increased toxicity in the longer chemotherapy group[23].

A study from Turrisi et al, where patients received four cycles of PE, highlighted the outcomes that may be achieved with short duration chemotherapy. Two-year survival for 419 patients with limited stage disease was 41–47%, and five-year survival was 16–26%[2].

APPROPRIATE NUMBER OF CYCLES OF CHEMOTHERAPY

Guideline – Small Cell Lung Cancer – Cycles of Chemotherapy	Level of Evidence	Refs
Four to six cycles of chemotherapy should be given.	II	2,21,22,23

DOSE ESCALATION OF CHEMOTHERAPY

In the 1970s, a clinical correlation was seen between chemotherapy dose and response, where patients received either cyclophosphamide 700mg/m^2 or 1 500mg/m^2, along with carmustine and methotrexate[24]. Subsequent trials have generally failed to confirm these findings. A meta-analysis of 60 randomised trials from the 1970s and 1980s investigated the role of dose intensity for a range of regimens. The range of variation in dose intensity was narrow. In extensive disease, there was no significant correlation between dose-intensity and survival, and results for limited disease were not consistent across regimens[25].

Ihde compared standard-dose and high dose PE in 90 patients with extensive stage SCLC. High-dose PE was delivered during the first two cycles only. A 46% increase in dose intensity did not improve outcome[26]. The dose-intense four drug CODE regimen (cisplatin, vincristine, adriamycin, etoposide), given over nine weeks, was compared with an 18 week OCA/PE regimen in a trial where 220 patients with extensive disease were randomised. Dose intensity was doubled, while the total dose of drugs delivered was the same for both arms. There were excessive treatment-related deaths in the CODE arm, and there was no difference in survival[27]. In a trial of similar design, CODE plus the cytokine G-CSF, was compared with alternating OCA/PE. Two hundred and twenty seven extensive stage disease patients were randomised and there was no difference in survival between the arms[28].

Positive results have been reported in a number of studies. In a small study of 63 patients with extensive stage disease, patients were randomised to receive CODE or CODE plus G-CSF. Dose intensity was increased in the G-CSF arm, with a significant improvement in survival, from 32 weeks to 59 weeks[29]. In a large study, 300 patients with good or intermediate prognosis were randomised to receive V-ICE (vincristine, ifosfamide, cisplatin, etoposide) either every three or four weeks. Patients were further randomised to receive either GM-CSF or no cytokine. GM-CSF did not alter the incidence of febrile neutropenia or the survival rate. Patients in the more intensive chemotherapy arm had improved survival (p=0.0014), with two-year survival increased from 18% to 33%[30]. In a similar design trial, 403 good prognosis patients were randomised to receive six cycles of adriamycin, cyclophosphamide and etoposide (ACE) at either two or three week intervals. Patients in the two-week interval arm also received G-CSF. The received dose intensity was increased 34% in the two-week arm, and survival was improved from 39% to 47% at 12 months[31]. Patients in the studies did not receive thoracic irradiation; similar results may have been obtained if radiation was included. Further studies are needed before a dose-intense approach may be considered to be standard therapy.

SECOND-LINE CHEMOTHERAPY

A frequent approach has been to treat with OCA on relapse following PE as first-line therapy, and vice versa. Where a good response was obtained with a first-line regimen, and the response was durable, 79% of patients responded to re-treatment with the same regimen in a small phase II study. The best results were obtained where there was a first-line complete remission and response duration was over eight months[32]. There have been no randomised studies comparing this approach to use of an alternative regimen. Topotecan has been compared to OCA as second-line therapy in a randomised trial, where patients relapsed at least 60 days after primary chemotherapy. There was no significant difference in response rate, time to progression or survival. Symptom control (dyspnoea, fatigue, anorexia, hoarseness, interference with daily living) was superior in the topotecan group[33]. A number of the other newer chemotherapy drugs have been shown to be efficacious for second-line therapy in SCLC, including paclitaxel[34] and irinotecan.

OPTIMUM SECOND-LINE CHEMOTHERAPY REGIMEN

Guidelines – Small Cell Lung Cancer – First and Second Line Chemotherapy	Level of Evidence	Refs
Where a platinum agent and etoposide have been given first line, then appropriate second-line regimens include the combination of cyclophosphamide, adriamycin and vincristine, or single agent topotecan. These regimens are of similar efficacy.	II	33
If first line chemotherapy has produced a response which has gone beyond eight months duration, it is reasonable to trial the first line drug again.	III–3	32

6.3 RADIOTHERAPY

CHEST RADIOTHERAPY IN LIMITED STAGE SMALL CELL LUNG CANCER

There is strong evidence for the role of thoracic radiotherapy in patients having 'radical' treatment for SCLC. This topic has been reviewed in a number of randomised controlled trials and meta-analyses[35,36,37]. Two meta-analyses were published in 1992 and both showed a benefit for thoracic radiotherapy. In the first analysis, the odds ratio for

benefit of radiotherapy on two-year survival was 1.52 ($p<0.001$) equating to a 5.4% increase in two-year survival. The addition of radiotherapy also improved local control by 25.3%, the odds ratio being 3.02 ($p<0.0001$). There was an excess of treatment related deaths in the combined treatment group with an odds ratio of 2.54 ($p<0.01$), but this only equated to a 1.2% difference in risk of treatment-related death. The second meta-analysis showed the same overall survival increase (5.4 ± 1.4%), but at three, not two years. The relative risk of death in the combined modality treatment group was 0.86 ($p=0.001$), corresponding to a 14% reduction in the mortality rate.

Most studies indicate additional benefit if the radiotherapy is given early rather than late[2,38,39,40,41,42,43] although in one randomised study (criticised for its methodology) there was no benefit for initial versus late chest irradiation[44]. A second randomised study showed no clear benefit for concurrent over sequential treatment[45]. The studies showing improved survival have generally used a total dose of at least 40Gy in 15Gy fractions over three weeks (or a biologically equivalent dose). Hyperfractionated thoracic radiotherapy has been shown in one large, fully published study to increase the long-term survival of patients with limited SCLC (five-year survival, 26% with hyperfractionated thoracic radiotherapy versus 16% with once daily radiotherapy). This was achieved with an increased rate of short-term Grade 3 esophagitis[2].

Guidelines – Small Cell Lung Cancer – Chemotherapy and Radiotherapy	Level of Evidence	Refs
In patients with limited stage small cell lung cancer, the addition of thoracic radiotherapy to standard combination chemotherapy improves overall survival and should be incorporated into a comprehensive treatment plan.	I	35,36,37
Thoracic radiotherapy should be offered early in relation to the course of chemotherapy rather than late. Evidence supports the administration of chemo-therapy concurrent with radiotherapy over sequential chemotherapy-radiotherapy administration.	II	2, 38, 39, 40, 41, 42, 43
Accelerated radiotherapy is associated with a survival advantage compared with standard fractionation.	II	2

PROPHYLACTIC CRANIAL IRRADIATION

There is strong evidence to recommend prophylactic cranial irradiation (PCI) for patients who have achieved complete remission following chemotherapy or chemoradiotherapy. Data from randomised controlled trials demonstrate that PCI decreases the frequency of brain metastases and increases disease free survival in these patients[46,47,48,49,50,51]. An individual patient data meta-analysis of seven randomised trials showed a relative risk of death in the treatment group as compared to the control group of 0.84 (p=0.01), an increased rate of disease free survival relative risk of recurrence of 0.75 (p<0.001) and a decreased cumulative incidence of brain metastasis (RR 0.46, p<0.001)[52]. The cumulative incidence of brain metastasis at three years was 58.6% in the control group compared with 33.3% in the treatment group.

There may be a dose-response relationship in SCLC and a dose of 30Gy in 3Gy fractions or 36Gy in 2Gy fractions is recommended. In the study reported by Gregor[47], PCI delivered as a dose of 24Gy in 2Gy fractions was no better than no PCI, while 36Gy in 18Gy fractions significantly reduced CNS relapse. Other studies have shown this benefit with doses varying from 24Gy in 8Gy fractions to 40Gy in 20Gy fractions[47,48,49,50,51].

On the basis of non-randomised data, it is recommended that PCI be given as soon as possible after patients achieve complete remission. Suwinski et al noted a threshold in dose-response when PCI was delayed, consistent with rapid growth of untreated sub-clinical disease in SCLC[53].

There is evidence from randomised controlled trials with data for up to 30 months of follow-up that PCI does not produce significant late neurotoxicity[46,47]. There is evidence from one randomised controlled trial that PCI does not have a detrimental effect on quality of life in the first 12 months following the completion of therapy. There is insufficient evidence to comment on the long-term effects of PCI on quality of life[47].

Guideline – Small Cell Lung Cancer – Prophylactic Cranial Irradiation	Level of Evidence	Refs
For patients who have achieved a complete response after induction therapy, prophylactic cranial irradiation is associated with a reduction in rate of brain metastases and prolongation of survival.	I	52

OTHER INDICATIONS FOR THORACIC RADIOTHERAPY

There is no evidence of any value in giving consolidation thoracic radiotherapy to patients with metastatic disease beyond the chest at presentation. The treatment from presentation onwards is palliative. The role of radiotherapy as a palliative modality conforms to palliation criteria in any disease entity or site.

Patients who are referred for consolidation thoracic radiotherapy after poor response to chemotherapy must have their histology reviewed as the first step in their management. If they are true SCLC, their prognosis is poor regardless of stage, with an expected median survival of two to three months only. Radiation therapy for these patients is palliative and is given when symptoms indicate.

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