Review Article

Follow up and surveillance post lung cancer surgery: a narrative review

Bejoy Philip[1]^, Anchal Jain[2]^, Pranav Ramesh[3]^, Naomi Melamed[4]^, Mashal Qureshi[5], Iqra Ahmed[6], Amer Harky[1]

[1]Department of Cardiothoracic Surgery, Liverpool Heart and Chest Hospital, Liverpool, UK; [2]Department of Cardiothoracic Surgery, Royal Stoke University Hospital, Stoke on Trent, UK; [3]School of Medicine, University of Leicester, Leicester, UK; [4]Department of Medical Education, St. George's University NHS Trust, London, UK; [5]School of Medicine, University of Liverpool, Liverpool, UK; [6]Department of Medical and Biomedical Sciences, St. George's University NHS Trust, London, UK

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Correspondence to: Mr. Bejoy Philip, FRCSEd (C-Th), MBA, DNB. Department of Cardiothoracic Surgery, Liverpool Heart and Chest Hospital, L14 3PE Liverpool, UK. Email: bejoyphilip@gmail.com.

Background and Objective: Lung cancer poses a significant global burden of disease, and whilst surgical and oncological therapies have revolutionised management, post-treatment recurrence remains a hurdle. Though there is no universal consensus which agrees upon a follow-up regime for these patients, evidence supports use of radiological imaging to monitor disease recurrence and progression. Through this narrative review, our objective is to compare current guidelines on follow-up and review the optimal imaging modality for follow up in lung cancer patients allowing for a more up to date review.

Methods: A comparative analysis of current guidelines in following-up patients after lung cancer resection such as American College of Chest Physicians (ACCP), the National Institute for Health and Care Excellence (NICE) and the European Society of Medical Oncology (ESMO) was performed to look at available recommendations. PubMed database was then used for literature search to identify published papers between 1992 and 2022 in English language. An analysis of relevant existing literature was then performed in the form of a narrative review.

Key Content and Findings: Although current guidelines mandate a patient-centred approach to care, they largely differ in their frequency and breadth of investigations at follow-up. The review looked at the various radiological modalities used for follow-up, their risks and benefits to the patients. We also reviewed the recurrence rates of the various pathological types of lung cancer and the disease free periods.

Conclusions: Lung cancer management must encompass several factors, including quality of life measurement as well as long-term monitoring with multidisciplinary team input. Whilst most studies favour the use of computed tomography (CT) for surveillance, it is clear there are several drawbacks that include exposing a patient to high dose radiation. There is scope for further studies which explore these factors.

Keywords: Lung cancer; follow up; staging; radiology; oncology

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^ ORCID: Bejoy Philip, 0000-0003-3662-7107; Anchal Jain, 0000-0002-2904-925X; Pranav Ramesh, 0000-0001-8936-7092; Naomi Melamed, 0000-0003-3396-2225.

Introduction

Worldwide lung cancer is the most common malignancy among men and third most common among women. It is the leading cause of cancer death worldwide, with mortality rates after 5 years reaching up to almost 90% (1). Non-small cell lung cancer (NSCLC) is the commonest subtype and surgery offers the best chance of cure. While surgery can achieve a curative state for patients with NSCLC, extensive recurrences are common with recurrence rates ranging from 30% to 50% (2). Small cell lung cancers (SCLCs) make up about 10% to 15% of the patients of the total number with lung cancers (3). SCLC is considered a systemic disease and a very aggressive form of cancer which is often widely disseminated on diagnosis. Janssen-Heijnen *et al.* studied the changes in treatment offered for SCLC and their outcome over 2 decades (4). They concluded that there had only been a modest increase in overall survival (OS) despite progress in treatment options and numbers.

Therefore, it is crucial to detect recurrences early in the disease course to increase the likelihood for further curative treatment. However, while recommendations for follow up have been suggested, there is a lack of a universally agreed follow up regime. As a result, various different surveillance regimes exist ranging from the combined use of chest X-ray and computed tomography (CT) to just CT alone (5,6). The primary aim of these follow-up regimes is the identification of local and distant recurrences. The ability to directly quantify the pattern of recurrence using imaging is beneficial in order to tailor specific therapies with the possibility of avoiding systemic therapies with a significant side effect profile. An example of this is in the treatment of oligometastatic NSCLC, where imaging studies have identified the majority of recurrences to be local, which therefore permits the shift of treatment to aggressive local therapy in addition to immunotherapy or targeted therapies (7). This is turn allows for a more effective and less toxic treatment regime. We present the following article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-22-28/rc).

Methods

A literature search of PubMed database was performed to identify relevant papers published between 1992 and 2022 in English language. Reference lists of relevant studies was also reviewed to identify additional papers. Key search terms such as “non-small cell lung cancer”, “surgery” and “radiological imaging”, were combined to generate a literature search. Notable exclusion criterion included animal studies or studies including a paediatric cohort. In order to evaluate current post lung cancer resection recommendations, a comparative analysis of guidelines was performed between American College of Chest Physicians (ACCP) (5), the National Institute for Health and Care Excellence (NICE) (8) and the European Society of Medical Oncology (ESMO) (6).

Discussion

Lung cancer surveillance

If lung cancer is detected early, the condition can be treated by surgical intervention. Other treatment modalities that may offer curative intent include chemo and radiotherapy. Despite these advances in modern medicine, recurrence is not uncommon and has been observed in up to one-third of this patient population (9). In addition, disease recurrence can be either symptomatic or asymptomatic in nature. Hence radiological follow-up is a useful tool for detecting local recurrence, second primary lung cancers and distant metastases which might not present clinically until the scope for curative treatment has diminished.

Stage-based treatment algorithms are followed to manage cancer recurrence based on the radiological findings from surveillance check-ups. Although many are not candidates for further surgical intervention, in some it is possible and may offer a cure and benefit to long-term survival if detected at an appropriate stage. For this reason, the use of various imaging modalities ranging from CT to positron emission tomography (PET) scan is supported in guidelines globally.

Patterns of recurrence

Classically, recurrences tend to occur at distant sites, with common locations including the pleura, contralateral lung, brain and bone (10). Boyd *et al.* explored the recurrence pattern of 250 patients with recurrence among a cohort of 975 patients undergoing surgery for NSCLC (11). The study demonstrated that 44% of recurrences were distant while 17% were local. Additionally, the median time for distant recurrences post-surgery was 12.5 months compared to 13.9 months for local recurrences. Likewise another study exploring local recurrences of NSCLC post-surgery, found a median time of 16.8 months to initial recurrence, with a median 2-year survival of 17.6% in these patients (12).

Table 1 A table to show the current guidelines regarding follow-up in lung cancer patients

Guidelines	NICE (8)	ACCP (5)	ESMO (6)
Frequency of follow-up	Specialist appointment 6 weeks after completing treatment	6 months for 2 years, then annually	6 months for 2 years, then annually
	"Regular appointment" following initial follow-up appointment		
Radiological follow-up	No recommendations	CT (CXR)	Extensive stage SCLC: CT every 2–3 months
			Limited stage SCLC: CT every 3–6 months
			Early NSCLC: every 6 months for 2 years
			Metastatic NSCLC: CT every 6–12 weeks
			Mesothelioma: to follow local guidelines
Further clinical assessment at follow-up	No recommendations	History	History
		Physical exam	Physical exam
		CXR	Smoking cessation
		Smoking cessation	

NICE, the National Institute for Health and Care Excellence; ACCP, American College of Chest Physicians; ESMO, the European Society of Medical Oncology; CT, computed tomography; CXR, chest X-ray; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

The disparity in median recurrence times between both studies may be due to differences in inclusion criteria. Boyd *et al.* recruited patients with stage 1 and 2 NSCLC whereas Hung *et al.* (12) exclusively recruited those with stage 1 NSCLC; thus, Boyd *et al.*'s (11) cohort suffers from an increased cancer burden, which could lead to increased likelihood of recurrence. Both studies, however, benefitted from modest sample sizes and follow up times, which in turn reduced the chance of type 2 error. The reasons for vast distant recurrences may be due to the presence of microscopic cancer cells which cannot be detected by routine staging and due to tumour handling during surgery resulting in cell dissemination (2,13).

Current recommendations

Several governing bodies including the ACCP (5), the NICE (8) and the ESMO (6) have provided guidelines for the follow-up of lung cancer, see *Table 1*. As the disease demonstrates great recurrence rates, it is imperative that all patients are followed up. However, there is no clear, universal consensus regarding exactly when and how these patients should be observed. Consequently, the current guidelines differ vastly. There is also ongoing debate, within the literature, around the choice of radiological modality. For example, the ACCP place emphasis on the use of chest X-rays with CT whereas ESMO guidelines centre on using CT scans alone.

Although these recommendations largely differ in their frequency and breadth of investigations at follow-up, all guidelines mandate a patient-centred approach to providing care to their patients. They also highlight the importance of patients maintaining their own surveillance checks. For example, NICE advocate the provision of clinic details, to enable patients to be "fast-tracked" to their treatment clinics if symptoms such as a cough or chest pain recur. These guidelines also place emphasis on smoking cessation therapy as an adjunct to follow-up care.

Evidence for radiological surveillance

Despite being well documented that lung cancer can recur in patients as both symptomatic and asymptomatic disease, there is only one prospective trial in the current literature that evaluates the effect of two follow-up programmes on OS. Westeel *et al.* randomised 1,775 patients with completely resected lung cancer of differing stages and subtypes. One arm consisted of a clinical exam and chest X-ray, whereas the other utilised a clinical exam, chest X-ray, chest and abdominal CT and bronchoscopy. Following a median follow-up of 8.7 years, no significant difference in OS or disease-free survival was demonstrated (14). However, it

is possible that a longer study follow-up could confer an increase in OS rates.

Other studies have addressed the effect of CT follow-up on OS in patients who received a lobectomy of NSCLC, demonstrating an increased survival due to the detection of local and distant recurrences at earlier stages (15,16). However, they also comment on the necessity of a CT-head to promote detection rate, which is a contentious issue when evaluating the cost-effectiveness of these programmes. In addition, single-armed prospective studies must take into account lead-time bias (whereby early diagnosis falsely appears to prolong survival). As definitive evidence evaluating OS is limited, further investigation is necessary to support current surveillance programmes that are frequently utilised to manage large patient sub-groups.

Recurrence rate for each tumour pathology

NSCLC, comprising adenocarcinoma, squamous cell carcinoma (SCC) and adeno-squamous carcinoma, is the most predominant subtype of lung cancer (85%) (1). However, there are limited studies which evaluate post-interventional recurrence rates in the subtypes for NSCLC. One study has shown that the recurrence rate of resected stage I lung adenocarcinoma (a subtype of NSCLC) was 17% (17). It was found that poor prognosis was linked to being male, smoking and tumour size with the lepidic histological subtype of adenocarcinoma possessing better survival (P=0.002) (18). Furthermore, guiding adjuvant therapy can be influenced by the subtype of lung adenocarcinoma as patterns of PL2 and micropapillary/solid predominant pattern have been shown to pose an increased likelihood of post-surgical recurrence (19).

Surgical intervention with curative intent remains the most definitive management for NSCLC, though recurrence rate remains high (20). However, a retrospective cohort study by Wang *et al.* found a 21.7% post-surgical recurrence in 1,387 subjects with stage 1 NSCLC (21). Risk factors which were statistically significant for poor prognosis (P<0.005) included: increased age, tumour stage 1B, histological classification and sub-lobar resection. This data is further supported by other studies mentioned earlier that depicted the overall NSCLC recurrence post resection to be 17% and 17.6% respectively (12,17).

These studies have established a correlation between factors such as smoking history, tumour size and nodal involvement and recurrence of early-stage NSCLC (12,17,21). Detailed histological analysis of subject cells as well as their function may be utilised to predict recurrence of early-stage NSCLC, for example Yu *et al.* has delineated a link between recurrence and nuclear and cytoplasmic morphology post-surgically in stage 1 of lung SCC and adenocarcinoma (22). Moreover, it has been postulated that aggressive tumour cells are more likely to aggregate in their functionality. Such studies pose a potential utility in mathematical analysis of lung tumour cells and their nuclei; this analysis has been useful in the context of breast, oropharyngeal and prostate cancers in predicting grade, recurrence and progression. Wang *et al.* also showed the potential of computerised histomorphological analysis of early-stage NSCLC cell samples post-definitive surgery and investigating nuclear architecture to be useful in predicting recurrence and outcomes (22).

Although large-cell neuroendocrine carcinoma (LCNEC) constitute only 2–3% of lung cancer cases, yet these are aggressive, difficult to diagnose and pose poor prognosis for its subjects (23). There is no definitive management for this subtype, however, there is a role for surgical resection, radiotherapy and adjuvant chemotherapy. Early recurrence of LCNEC is common, with 63.9% recurrence 1-year post-surgery and 91.7% 3 years post-surgery (24). Optimistically, the addition of adjuvant chemotherapy was shown to have an 88.9% rate of 5-year OS compared to the control group (47.4%) (25). However, it is important to note that these studies (24,25) are a single centre study with a very small population size. We need evidence from a much larger number of subjects to increase reliability and validity of such data.

Constituting approximately 1% of all lung tumours, carcinoid lung cancers have conveyed good long-term response to surgical resection. Okereke *et al.* conducted a 12-year retrospective review of 121 patients who were treated with surgical resection of lung carcinoid tumours demonstrated a 5-year survival of 93% (26). It is generally not recommended for chemotherapy to be used in the management of carcinoid tumours (27); this is concordant with Okereke *et al.* which found that all patients who underwent chemotherapy experienced a recurrence in their typical carcinoid tumour.

SCLC, which is considered an aggressive form of lung cancer is mostly treated with chemotherapy, radiotherapy and prophylactic cranial radiotherapy. SCLC is usually classified as limited stage and extensive stage. Patients with limited stage SCLC, in which tumour is limited to a part of the lung, can be offered surgical resection if fit for surgery. Most patients following surgical resection undergo

Table 2 Recurrence rates and disease-free survival (5 years) in NSCLC

TNM stage (8th Edition)	Recurrence (36) (%)	Disease-free survival (37) (5 years) (%)
IA	33.9	50–80
IB	37.8	47
IIA	61.2	36
IIB	57.9	26
IIIA	62.8	19
IIIB	35.8	7

NSCLC, non-small cell lung cancer; TNM, tumor, nodes, and metastases.

chemotherapy and radiotherapy as well when diagnosed with SCLC. A review article by Low *et al.* published in 2018 found that patients with stage 1 SCLC who underwent surgical resection followed by chemotherapy had improved survival than patients who had chemotherapy alone (28). In a recent paper published by Rudin *et al.*, they mention that in patients who underwent surgical resection of SCLC followed by chemotherapy there was 35% increase in 5-year survival rates (29). The NCCN guidelines recommend prophylactic cranial irradiation as standard management for patients as reduces the risk of metastasis and improves survival (30). In a review paper, Johnson mentions that patients who have been treated for SCLC have a 6% per patient per year risk of developing NSCLC (31). As SCLC is also associated with tobacco there is a high risk of developing a second malignancy in the lungs or other organs as shown in studies (32).

A single-centre trial showed that LC first recurrence was predominantly distant disease; this was common across the SCLC and NSCLC cases, as well as amongst those who received systemic chemotherapy and local therapy. It was found that the most common location of distal metastasis comprised the central nervous system. Furthermore, those with higher-stage cancers, unsurprisingly, had higher rates of recurrence (33).

Tumour staging

The predominantly used tumour staging system used for NSCLC is the American Joint Committee on Cancer (AJCC) tumor, nodes, and metastases (TNM) system. This is based upon the following: tumour size and extent (T), degree of cancer spread to lymph nodes (N) and metastasis (M) (34).

A retrospective analysis undertaken by Yun *et al.* analysed 3,950 patients between 2006 and 2015 who had undergone complete resection and lymph node clearance for NSCLC (35). Both OS and recurrence-free survival was lower between TNM stages IA to IIIA. This prognostication was further corroborated by all hazard ratios (HRs) between contiguous TNM staging groups being greater than 1. Notably, however, between stages IIA and IIB, there was no significant difference in either OS or recurrence-free survival which was consistent in the 8th edition of the TNM scoring system. *Table 2* demonstrates the correlation between TNM staging, recurrence rates and disease free survival.

Optimum imaging for follow-up

CT

Despite there being no high-quality evidence for CT surveillance, treatment of recurrence has changed significantly over the last few years which may make the early detection of recurrence more important in the modern era.

Current guidelines from the ESMO recommend a history and physical exam every 6 months for 2 years and additionally a contrast enhanced chest CT scan at 12 months then 24 months (38). Additionally, in patients suitable for salvage treatment options a CT scan every 6 months for 3 years is recommended (III, B). The recommendation of CT scanning over conventional chest X-ray (CXR) may be amendable to the increased sensitivity to detect asymptomatic recurrences (39). In-fact, Westeel *et al.* (15) demonstrated that six monthly CT scans detected a greater number of recurrences, which could be treated with curative intent, compared to physical examination and CXR in a cohort of individuals with NSCLC. A common cause of initial surgical treatment failure in individuals with NSCLC are brain metastases. One observational study demonstrated that synergistic use of CT chest and CT head drastically improved detection rates of brain metastases and thus increased OS post lobectomy (16). However, with such an intensive CT regime this study would have benefitted from a cost utility analysis as it would be necessary to identify whether the added cost and subsequent early recurrence recognition translates to a better quality of life within the patient population. One meta-analysis found that intensive follow up using CT imaging resulted in increased survival rates among those with asymptomatic recurrent NSCLC [HR =0.61 (0.50–0.74), P<0.01] (40). However, these results must be interpreted with caution

due to significant heterogeneity in follow-up regimes between studies and a significant lack in the inclusion of robust randomised control trials [eight observational studies and one randomized controlled trial (RCT) formed the meta-analysis]. Another observational study demonstrated an increased sensitivity for minimal dose CT for the diagnosis of recurrent NSCLC compared to CXR alone (94.2% versus 21.2%, P<0.001) (41). One potentially large disadvantage for the use of CT imaging is the increased radiation exposure (~10.0 mSv) which can result long term complications. However, this may be offset by the use of minimal dose CT imaging which have a similar effective radiation dose to conventional CXR (0.2 mSv versus 0.16 mSv respectively) (41). While the majority of evidence favours CT imaging for the diagnosis of recurrent NSCLC, there is still a lack of robust sufficiently powered RCT data.

PET

Current guidelines from NCCN recommend the use of fluorodeoxyglucose (FDG) PET/CT for the staging of a primary NSCLC but its use for diagnostic follow-up is not recommended routinely. Nonetheless, studies have demonstrated a greater accuracy of diagnosis of recurrences with a FDG PET/CT compared to a CT alone with sensitivities and specificities ranging between 95–100% and 78–80% respectively (42,43). However, it is important to note that the ability of PET/CT to detect brain metastases is grossly limited due to the inherently high glucose uptake and usage within the brain (44). Interestingly, in a cohort of patients with stage III NSCLC, Reddy *et al.* (45) found no decreased recurrence detection time or improved survival using PET/CT compared to contrast enhanced CT alone. This evidence, while contradictory to the multiple studies favouring PET/CT, seems to support the NCCN guidelines of not routinely recommending PET/CT. One possible reason for the lack of significant difference may be due to imaging protocol differences. In Reddy *et al.*'s study, the local CT imaging protocol involved an extension of the CT scan to include the upper abdomen, thus including the liver and adrenal glands, organs where lung cancer metastases are commonly found (45).

Magnetic resonance imaging (MRI)

Currently, routine use of MRI for follow up of recurrent disease is not recommended and instead CT and PET-CT are preferred, especially where radical treatment can been performed (46). However, this may, in part, be due to the limited evidence exploring the capabilities of MRI in this patient population. Despite this, one study validated the use of MRI for the detection of hilar, mediastinal and pulmonary vasculature invasion in cases of bronchogenic carcinoma (47). Additionally, in cases where CT is unable to distinguish smaller degrees of invasion, MRI has been shown to have an important role (46). Lee *et al.* (48) compared the accuracy of whole-body MRI to PET-CT in a cohort of sixty-two participants with NSCLC. The study found that both imaging modalities had an identical sensitivity of 85.71% and good correlation to assess malignant recurrences (γ=0.86; P<0.01). This result alongside the added benefits of no ionising radiation and excellent tissue characterisation demonstrates clinical potential for the use of MRI post lung cancer surgery.

Stage-based follow-up

An observational study found that 25% of 1,294 patients with NSCLC who underwent routine CT surveillance were subjected to false-positive results and required subsequent investigations (10). Furthermore, a randomised trial conducted by Westeel *et al.* compared maximal and minimal radiological surveillance and follow-up and found that there was no significant survival benefit conferred by maximal surveillance (14,49). Korst *et al.* found that false-positive CT results were found in 50% of patients with Stage I–IV disease (50) and a further 4–5% underwent subsequent invasive procedures (10,50). Following patients up should be guided by patient preference, clinical picture and the prospect of whether further intervention will be implemented. Though it is critical that this research is repeated on a large, multi-centre scale, one may question the utility and cost benefit of radiological surveillance when evidence supporting it is poor.

Dealing with recurrence

Despite there being no high-quality evidence for CT surveillance, treatment of recurrence has changed significantly over the last few years which may make the early detection of recurrence more important in the modern era.

The Stereotactic Ablative Radiotherapy (SABR) trial is an international, multi-centre randomised trial which hypothesised that patients with primary malignancy and oligometastatic cancer may be cured from targeting all lesions (51). It was found that SABR was associated with increased OS; median OS was 28 months in the control group as opposed to 41 months in the SABR group. The

results of these preliminary trials are positive and could pose really promising outcomes for patients who undergo ablative radiotherapy, however, further phases are required to ascertain the maximum quantity of oligometastatic lesions that can be targeted by SABR, as well as to conclusively determine OS (51).

We can utilise our knowledge of the dysregulation of signalling pathways and oncogenes in NSCLC to target therapies, with many novel strategies emerging. Anaplastic lymphoma kinase (ALK) inhibitors, for example, crizotinib has emerged as an effective NSCLC treatment; however, issues emerged concerning mutations and lack of potency in targeting ALK which can cause relapse of NSCLC (52). However, phase 3 trials are being developed to target the limitations of preceding ALK inhibitor therapies with some potentially promising outcomes (53). Further oncogenic targets have been identified including: epidermal growth factor receptor (EGFR), c-ros oncogene 1 (ROS1), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF). However, similar to ALK inhibitors, the issue of mutation-related resistance as well as difficulties in treating metastatic cancer means it is more imperative than ever to uncover and target previously-unknown oncogenes (54).

Management of recurrence can be tailored according to the patient's presentation. Patients who are asymptomatic deem to have a better prognostic outcome over symptomatic patients. A review by Gourcerol *et al.* established that asymptomatic patients were more likely to be offered treatment, in particular, curative treatment (55). They also noted an increase in survival in asymptomatic patients from time of recurrence as opposed to the symptomatic group. This was supported by a retrospective review which found that median OS was greater in asymptomatic cases as opposed to symptomatic cases (15.5 *vs.* 7.2 months; P=0.001) (55).

Treatment can be categorised into curative and palliative. Recurrence can be intrathoracic or extrathoracic and the location of disease recurrence is important when formulating a management strategy (55). Another factor to acknowledge when deciding management options for recurrence is the treatment used for the primary lung cancer; patients often undergo aggressive treatments for the primary cancer thus their tolerance of side effects is reduced for treatment used for recurrence.

For oligometastatic recurrence of lung cancer, first line treatment deemed appropriate is surgical resection and radiotherapy. For locoregional recurrence, radiation is more beneficial for disease control. A prospective study by Yano *et al.* assessed the progression free survival (PFS) in patients with oligometastatic recurrence and administered local treatment consisting of surgery and radiotherapy. They found that the median PFS was greater for local treatment for oligometastatic recurrence at 20 months as opposed to systemic treatment (56).

In locoregional recurrence, treatment begins with radiation, however when unsuccessful, treatment shifts to palliative. However, a review by Dickhoff *et al.* examined salvage surgery following radiation in persistent NSCLC; 158 patients were assessed with 152 undergoing surgical resection. The data reported a 30-day mortality of 3% and a 90-day mortality of 6.5%, demonstrating the advantages of surgical resection following radiation. A small patient cohort was assessed thus the data is not representative for the affected population, nevertheless, it indicates the evolving nature of recurrence management (57). Furthermore, a recent case series examining salvage surgery in NSCLC recurrence reports of OS of 25 months following surgery, noting that salvage surgery is feasible (58). However, stronger evidence with a lower risk of bias in the form of a robust RCT is required due to the high heterogeneity of patients.

Not all patients are deemed appropriate for salvage surgery, patients must be fit for surgery, tumour must appear resectable and no distance metastases must be present (57).

When patients are not suitable, alternatives can be used such as re-irradiation (reRT). However, reRT can be challenging due to the toxicity risk it poses. A recent study assessed the use of reRT in 33 patients for recurrent small-cell lung cancer. They concluded reRT doses >40 Gy to be used as an effective palliative treatment as a median OS rate of 7 months was noted, albeit in a small sample (59). This claim is further supported by a report which saw 75% of their cohort with NSCLC achieving palliative benefit from reRT (60).

At present topotecan has been favoured as a chemotherapy agent for management of recurrent SCLC (61). Horita *et al.* noted disease control in 42% of cases and an OS rate of 57% at 6 months in a cohort of 1,347 patients. However, new therapy agents are being explored (62). Recently, Baize *et al.*, examined the use of carboplatin and etoposide against topotecan for relapsed SCLC. They discovered that the median PFS was significantly greater in the dual therapy group as opposed to the topotecan group, 4.7 *vs.* 2.5 months (P=0.0041). Furthermore, a greater proportion of the topotecan group

suffered from adverse effects as opposed to the combination group (63).

Monotherapies of docetaxel, pemetrexed or erlotinib can be used against recurrent NSCLC. However, the effectiveness of dual therapies is being explored. Reck *et al.* concluded that the use of dual therapy of docetaxel and nintedanib against docetaxel for recurrent NSCLC was effective especially for adenocarcinoma. A cohort consisting of 1,314 patients was used. PFS was significantly longer in the dual therapy group (3.4 *vs.* 2.7 months; P=0.0019). In the population with adenocarcinoma histology, median OS was greater in dual therapy cohort (12.6 *vs.* 10.3 months; P=0.0359), but no difference in OS was noted in other histological groups (64).

Immunotherapy is an emerging treatment for the management of recurrent lung cancer. Nivolumab, atezolizumab and pembrolizumab have displayed promising results in terms of OS outcomes when compared with docetaxel (65). Histological subtype analysis between nivolumab and docetaxel demonstrated that OS for nivolumab was greater in squamous NSCLC (65).

A randomised control trial evaluating combined immunotherapy with nivolumab and ipilimumab verses chemotherapy in patients with advanced NSCLC suggests an increased OS with immunotherapy. The study cohort was split into patients with programmed death-ligand 1 (PD-L1) ≥1% and PD-L1 <1%. Global improvement was seen; 4-year OS rate with combined immunotherapy verses chemotherapy was noted at 29% versus 18% (PD-L1 ≥1%) and 24% verse 10% respectively (PD-L1 <1%) (66). In terms of efficacy, an improved was seen in the combined immunotherapy group compared with nivolumab monotherapy. These preliminary results are promising, however further trials are required to evaluate the efficacy of combined immunotherapy and ascertain their use in treatment of recurrence (66).

A single centre retrospective analysis has demonstrated encouraging results when combining reirradiation with immunotherapy to treat recurrence; 43% of the study cohort was treated only with reirradiation and 57% received systemic therapy with reirradiation. The immunotherapy subgroup displayed the highest median OS at 21.8 months (95% CI: 17.8–25.8 months) compared with 18.9 months (95% CI: 16.5–21.3 months). The results hypothesizes that immunotherapy can improve the effectiveness of reirradiation. Despite these promising results, further trials are required using larger cohort sizes to strengthen the association as these results were based on a small cohort of 47 patients (67).

Future plans and studies needed

Findings from this review can be used to influence the development of future studies. Further research would assist in consolidating the ideas explored in this review.

Ideally, further examination into the use of CT imaging for recurrence in asymptomatic NSCLC needs to be explored by formulating a meta-analysis including studies with low heterogeneity and ensuring a high amount of randomised control trials are provided. Future studies can include the development of robust randomised control trials investigating CT scans in asymptomatic follow up as it would assist in consolidation of data.

As aforementioned, the NCCN guidelines state that at present they do not recommend routine use of PET scans in diagnosis of recurrent lung cancer, despite evidence suggesting that these scans provide a greater accuracy at diagnosing recurrence (30). Future studies should include a review and further RCTs into the use of PET scans to strengthen the association discovered and would enable review of the NCCN guidelines.

Moreover, development of a national or international database outlining the imaging used for diagnosis and management used in recurrent lung cancer would be of great clinical significance, as it would contribute to improving the management of this patient cohort. A national database would be generalizable to the population.

In terms of management options, further insight is required into the use of salvage surgery as a treatment option for NSCLC recurrence as at present the research available is of high heterogeneity.

Currently, there are minimal studies into the use of reRT for recurrence of lung cancers, however they have been promising. To further evaluate the cause, more randomised control trials with large patient cohorts are required. Further research into different management options will allow clearer clinical outlines for intervention in patients with recurrence. Finally, a study design exploring disability-adjusted (DALY) and quality-adjusted life years (QALY) in the palliative population with recurring lung cancer should be formulated to evaluate if quality of life is improved and which treatment option provided the greatest improvement in quality of life.

Conclusions

Radiological surveillance post oncological therapy is an important element of patient care for lung cancers. Despite

governing bodies around the world issuing guidelines on specific modalities of radiological techniques and timings for follow-up, only one randomised control trial has attempted to delineate the effect of two different surveillance programmes on OS. Nevertheless, observational studies describe the advantages of radiological modalities including CT, PET and MRI. Whilst most studies favour the use of CT for surveillance, it is clear there are several drawbacks that include exposing a patient to high dose radiation. Further investigation is required to determine the usefulness of current programmes.

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Footnote

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