Neoadjuvant chemotherapy in lung cancer

Lung cancer is the most commonly diagnosed cancer and is also the leading cause of cancer-related mortality in the USA. More people die from lung cancer than from colorectal, breast and prostate cancers combined. Patients with early-stage lung cancer are treated with surgery, which is followed by adjuvant chemotherapy in stage II and IIIA patients. Neoadjuvant chemotherapy in early-stage lung cancer has been evaluated in many clinical trials with variable results, and the current standard of care for early-stage lung cancer is surgery followed by adjuvant chemotherapy. Patients with locally advanced lung cancer are treated with definitive concurrent chemoradiotherapy. The role of neoadjuvant chemotherapy in this setting has been explored in many clinical trials. Two meta-analyses have demonstrated that neoadjuvant chemotherapy is beneficial in patients with locally advanced lung cancer; however, a large Phase III clinical trial failed to show survival advantage with neoadjuvant chemoradiotherapy followed by surgery compared with chemoradiotherapy alone in locally advanced lung cancer. Therefore, there is no established role of neoadjuvant chemotherapy in early-stage lung cancer and its role in locally advanced lung cancer is still being investigated.

KEYWORDS: early-stage lung cancer ■ locally advanced lung cancer ■ lung cancer ■ neoadjuvant chemotherapy ■ targeted therapy

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According to the 2010 estimate by the American Cancer Society, lung cancer is the most commonly diagnosed cancer in the USA, with an estimated 222,520 new cases of lung cancer diagnosed every year, and is also the leading cause of cancer-related mortality, with an estimated 157,300 people dying from lung cancer every year [1]. More people die from lung cancer than from breast, prostate and colorectal cancers combined, and more women die every year from lung cancer than from breast cancer [1].

Based on Surveillance, Epidemiology and End Results (SEER) estimates, most patients (50%) with lung cancer have advance-stage or stage IV disease by the time of their diagnosis. Approximately 16% have localized disease and 25% have locally advanced disease [101].

The estimated 5-year survival for lung cancer has hardly changed in the past 30 years and is only 16%, which is much lower than other major cancer types such as breast, colorectal and prostate [101]. Even when compared stage for stage, the 5-year survival for lung cancer is much less than other corresponding major cancer types (Figure 1).

Thus, not only are newer agents needed in the treatment of lung cancer, but also attempts are underway to modify current treatment options to obtain better outcomes. In this regard, neoadjuvant chemotherapy has been evaluated in various studies. In this article, we focus on some of those studies and suggest future directions.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is used in many cancer types prior to definitive local treatment, either in the form of surgery or radiation. The potential advantage of using such an approach is to target occult microscopic disease at the earliest possible time in cancer treatment. In addition, neoadjuvant chemotherapy results in shrinkage of the primary tumor, which not only gives an *in vivo* assessment of the tumor's chemosensitivity, but also potentially reduces the risk of definitive surgery. Furthermore, neoadjuvant chemotherapy is likely to be better tolerated than similar adjuvant treatment.

The disadvantages of such an approach include a delay in potentially curative surgery, less accurate staging and an increase in surgical morbidity and mortality.

Treatment for early-stage lung cancer

Patients with early-stage lung cancer (stage I and II, and some stage IIIA) are treated with surgery. Patients who are deemed resectable and are medically fit enough to undergo surgery should be offered lobectomy or

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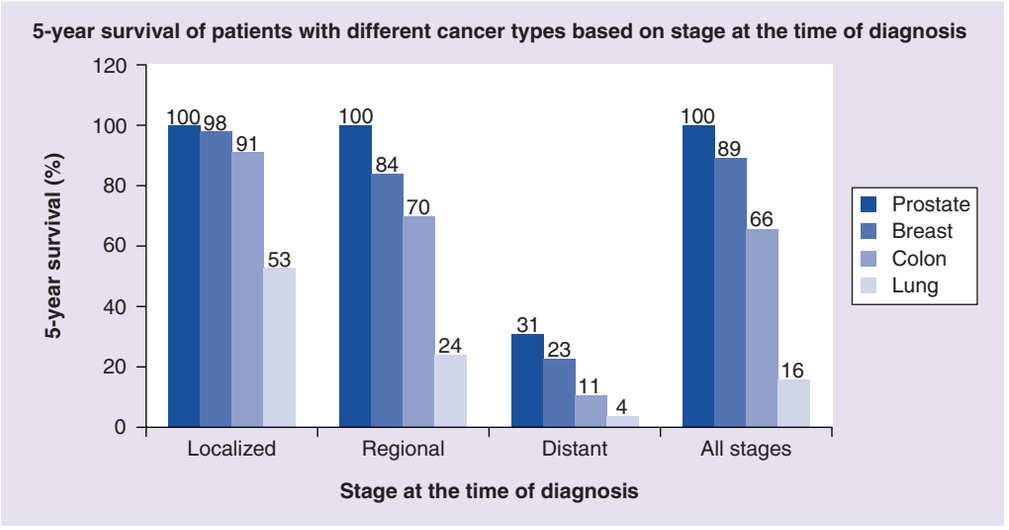

Figure 1. Estimated 5-year survival rate of patients with different cancer types based on stage at the time of diagnosis. Overall lung cancer has the poorest 5-year survival rate. Stage-for-stage survival for lung cancer is much lower compared with other major cancer types. Data taken from [1].

greater resection (category IA recommendation from the American College of Chest Physicians [ACCP] Evidence-Based Clinical Practice Guidelines, 2nd Edition) [2]. Adjuvant chemotherapy has been evaluated in many clinical trials, and has been found to be useful in stage II and IIIA lung cancer after surgical resection [3,4]. Recently updated results of th Cancer and Leukemia Group B (CALGB) 9633 trial were reported. This was a randomized trial comparing adjuvant chemotherapy with observation in patients with resected stage IB non-small-cell lung cancer (NSCLC). Overall, there was no survival advantage but an exploratory analysis demonstrated a significant survival advantage in favor of chemotherapy for patients with tumors of more than 4 cm (hazard ratio [HR]: 0.69; CI: 0.48–0.99; p = 0.043) [5].

The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis was based on the five largest adjuvant chemotherapy clinical trials in lung cancer, involving 4584 patients, and demonstrated an absolute survival advantage of 5.4% in favor of chemotherapy with the largest benefit to stage II and III patients [6].

More recently, two meta-analyses were published in the same article evaluating the role of adjuvant chemotherapy in lung cancer. The first meta-analysis, based on 34 trials, compared surgery plus chemotherapy versus surgery alone and found an absolute increase in survival of 4% at 5 years with an HR of 0.86 (95% CI: 0.81–0.92; p < 0.0001) with the addition of adjuvant chemotherapy compared with surgery alone. The second meta-analyses, published in the same article, based on 13 trials, evaluated the addition of chemotherapy to surgery plus radiotherapy as opposed to surgery plus radiotherapy alone. The addition of chemotherapy to surgery plus radiotherapy also provided an absolute survival advantage of 4% at 5 years, with an HR of 0.88 (95% CI: 0.81–0.77; p = 0.009) [7]. Therefore, adjuvant chemotherapy after surgery, for patients with operable NSCLC, improves survival irrespective of whether chemotherapy was used with surgery alone or adjuvant to surgery plus radiotherapy.

Neoadjuvant chemotherapy in early-stage lung cancer

Neoadjuvant chemotherapy has been evaluated in many clinical trials in lung cancer. In one such large randomized Phase III clinical trial from Europe, 519 patients with early-stage lung cancer were randomized to undergo surgery or receive three cycles of neoadjuvant chemotherapy followed by surgery. The patients were offered any of six platinum-based chemotherapy regimens. In this clinical trial, 61% of patients were stage I and 31% were stage II. This trial demonstrated that neoadjuvant chemotherapy was feasible as 75% of the patients received all three cycles of chemotherapy and an additional 14% received two cycles. It resulted in a good response rate (49%) and down-staging (31%) of tumors. In addition, neoadjuvant chemotherapy did not increase postoperative complications; however, there was no evidence of a benefit in terms of overall survival (HR: 1.02; 95% CI: 0.81–1.31; p = 0.86) [8].

Two similar studies, one from Europe and the other from the Southwest Oncology Group (SWOG), evaluating the role of neoadjuvant chemotherapy in early-stage lung cancer, were initiated. The results of one of these studies (SWOG S9900) were recently published and demonstrated an improvement in overall survival with preoperative chemotherapy (HR: 0.79; 95% CI: 0.60–1.06; p = 0.11). However, both studies were closed early once a survival advantage from adjuvant chemotherapy was demonstrated in multiple clinical trials and it was no longer considered ethical to have a surgery-alone arm [9,10].

To address whether neoadjuvant chemotherapy or adjuvant chemotherapy prolong disease-free survival as compared with surgery alone, a large Phase III trial was recently published [11]. In this trial, 624 patients with stages IA, IB, II or T3N1 were randomly assigned to surgery alone (212 patients), three cycles of preoperative paclitaxel–carboplatin followed by surgery (201 patients) or surgery followed by three cycles of adjuvant paclitaxel–carboplatin (211 patients). The primary end point was disease-free survival. In the preoperative arm, 97% of patients started the planned chemotherapy and radiological response rate was 53%. In the adjuvant arm, 66.2% started the planned chemotherapy. A total of 94% of patients underwent surgery and surgical procedures, and postoperative mortality was similar across the three arms. Patients in the neoadjuvant chemotherapy arm had a nonsignificant trend towards longer disease-free survival than those assigned to surgery alone (5-year disease-free survival: 38.3 vs 34.1%, respectively; HR for progression or death: 0.92; p = 0.176). The 5-year disease-free survival rates were 36.6% in the adjuvant arm versus 34.1% in the surgery arm (HR: 0.96; p = 0.74). This trial demonstrated no advantage of neoadjuvant or adjuvant chemotherapy over surgery alone; however, approximately two-thirds of the patients in this trial had stage I disease, for which there are no data that adjuvant chemotherapy is beneficial. Therefore, it is difficult to draw any conclusions from this clinical trial.

Thus, patients with early-stage lung cancer should undergo surgery followed by adjuvant chemotherapy. Neoadjuvant chemotherapy in early-stage lung cancer may improve survival but needs further investigation.

Treatment for locally advanced lung cancer

Locally advanced or stage III NSCLC represents a heterogeneous group of patients who require a multimodality approach for their management, involving various subspecialties. Stage IIIA includes patients who are incidentally found to have N2 disease at the time of surgery (i.e., microscopic N2) and are treated the same as early-stage patients with surgery followed by adjuvant chemotherapy [12]. Benefit of postoperative radiotherapy (PORT) in resected N2 patients is controversial and has been difficult to prove [13].

Stage III patients with bulky N2 or N3 disease are treated with concurrent chemoradiotherapy [14]. Adding three cycles of consolidation chemotherapy after concurrent chemoradiotherapy was evaluated in a Phase III clinical trial, which demonstrated no survival advantage with additional chemotherapy [15].

Neoadjuvant chemotherapy in locally advanced lung cancer

The role of neoadjuvant chemotherapy in locally advanced lung cancer was evaluated in a clinical trial in which a total of 156 patients were given three cycles of induction chemotherapy consisting of navelbine, ifosfamide and cisplatin (NIP) followed by surgical resection [16]. After surgery, patients were randomized to an additional two cycles of the same chemotherapy or observation. A total of 65% of patients in this study had stage IIIA disease, 7% had stage IIIB disease and 28% had stage IIA. The study was closed early owing to poor accrual, but gave some interesting results. The overall response rate for chemotherapy was 52.6% with a 3.2% clinically complete response. A complete resection (R0) was possible in 74% of the patients and down-staging from N2 to N0 was seen in 29% of the patients. After a median follow-up of 48 months, the median survival was 31.8 months in patients who also received two additional cycles of adjuvant NIP and 32.3 months in those who did not receive additional adjuvant NIP. Although patients were not randomized based on neoadjuvant chemotherapy this trial gives an impressive overall survival of over 30 months in stage III patients with neoadjuvant chemotherapy.

Another Phase III trial conducted by the French Thoracic Cooperative Group included 373 patients with stage I, II and IIIA resectable NSCLC [17]. Patients were randomly assigned to surgery alone or two cycles of mitomycin, ifosfamide and cisplatin preoperatively, followed by surgery and two additional postoperative chemotherapy cycles in responding patients. PORT was given for pT3 or pN2 and/or incomplete resection. In this trial, a total of 167 patients (47%) were stage IIIA. Median survival was 37 months in the perioperative chemotherapy arm and 26 months

in the surgery alone arm, and this was reported not to be statistically significant (p = 0.15). Statistically significant survival advantage was only observed in stage I and II patients with no survival advantage of perioperative chemotherapy seen in stage III (N2) patients.

In another Phase III randomized trial, the role of induction chemotherapy was evaluated prior to surgical resection or definitive radiation [18]. Patients with histologically proven stage IIIA N2 NSCLC were given three cycles of platinum-based induction chemotherapy. Responding patients were then randomized to surgical resection or radiotherapy. A total of 167 patients were allocated to the resection and 165 to the radiotherapy arms. A total of 42% of the patients had pathological down-staging and 5% had a pathologically complete response. In the surgery arm, 40% of patients also received PORT. Median and 5-year overall survival for patients randomly assigned to resection versus radiotherapy were similar at 16.4 versus 17.5 months and 15.7 versus 14%, respectively (HR: 1.06; 95% CI: 0.84–1.35). Rates of progression-free survival were also similar in both groups. The results of this trial are difficult to interpret as almost half of the patients in the surgery arm also received PORT.

Meta-analyses of neoadjuvant chemotherapy in locally advanced lung cancer

To date, two meta-analyses, based on data extracted from publications, have been reported, evaluating the role of neoadjuvant chemotherapy in NSCLC (Table 1). In the first of the two meta-analyses by Burdett *et al.*, seven randomized controlled trials (RCTs), involving a total of 988 patients, were included [19]. In these trials, patients were randomized between preoperative chemotherapy followed by surgery or surgery alone. Survival data was available for all seven RCTs. The combined results demonstrated that a significant increase in survival was associated with the use of preoperative chemotherapy (p = 0.02). The HR of 0.82 (95% CI: 0.69–0.97) represents an 18% relative reduction in the risk of death with preoperative chemotherapy. This is equivalent to an absolute improvement of 6% at 5 years, increasing overall survival from 14 to 20%. The criticism of the this meta-analysis is that the confidence intervals for individual trials were very wide and only two trials had more than 100 patients in each arm, while the other five had less than 50 patients in each arm. In these trials, survival across all stages showed an absolute benefit from addition of preoperative chemotherapy.

The second of these meta-analyses by Song *et al.* encompasses a total of 13 RCTs, including the seven reported in the meta-analyses by Burdett *et al.* and four additional RCTs from China [20]. The total number of randomized patients in these clinical trials was 3224, with 1637 in the neoadjuvant chemotherapy arm and 1587 in the surgery alone arm. Platinum-based regimens of neoadjuvant chemotherapy were used in all eligible clinical trials. The individual HRs of nine trials were in favor of chemotherapy plus surgery, whereas those of the other four trials were in favor of surgery alone. The combined HR of these trials is 0.84 (95% CI: 0.77–0.92), which is a statistically significant result (p = 0.0001) and, as a whole, is in favor of neoadjuvant chemotherapy. Two of the largest trials included in this meta-analysis were from China and only included stage III patients [21,22]. In the sub-group analysis of stage III patients, 823 were randomized to neoadjuvant chemotherapy followed by surgery and 763 were randomized to surgery alone. The combined HR of neoadjuvant chemotherapy in stage III patients was 0.84 (95% CI: 0.75–0.95), illustrating that neoadjuvant chemotherapy benefitted stage III NSCLC patients significantly (p = 0.005). These two meta-analyses clearly demonstrate the benefit of neoadjuvant chemotherapy in locally advanced lung cancer.

Some of the largest trials in this meta-analysis only included stage III patients. The control arm in these trials was surgery alone, which is not the standard of care for stage III patients. There is clear survival benefit with use of adjuvant chemotherapy in stage III patients. Therefore, it is difficult to state conclusively that neoadjuvant chemotherapy provides additional survival benefit as opposed to giving the same chemotherapy in an adjuvant setting. A better designed clinical trial should randomize stage III lung cancer patients between neoadjuvant and adjuvant chemotherapy to find out which treatment approach is more feasible, effective and safer in stage III lung cancer patients.

Table 1. Published meta-analyses of neoadjuvant chemotherapy in non-small-cell lung cancer.

Author (year)	n of clinical trials	n	HR (95% CI)	Ref.
Burdett *et al.* (2006)	7	C + S = 493 S = 495	0.82 (0.69–0.97)	[19]
Song *et al.* (2010)	13	C + S = 1637 S = 1587	0.84 (0.77–0.92)	[20]

Two published meta-analysis show benefit of neoadjuvant chemotherapy in non-small-cell lung cancer with an HR of <1.
C: Chemotherapy; HR: Hazard ratio; S: Surgery.

Neoadjuvant chemotherapy & radiation therapy in locally advanced lung cancer

The role of radiation in addition to neoadjuvant chemotherapy – either concurrent or sequential – has been evaluated in several clinical trials. A Phase II clinical trial was conducted in Japan, in which patients with bulky N2 and N3 disease were treated with induction chemoradiotherapy followed by surgery [23]. A total of 41 patients with stage IIIA and IIIB disease were treated with two cycles of either carboplatin–paclitaxel or carboplatin–docetaxel concurrent with radiation (50 Gy) followed by surgical resection. The overall response rate to chemoradiotherapy was 78% with a complete pathological response of 17.1%. There was no progressive disease and surgery could be performed in all 41 patients with complete resection of the tumor. A major response (less than a third of cancer cells viable in the pathology samples) was achieved in 56.1% of cases. A minor response (more than two-thirds of cancer cells viable in the pathology samples) was observed in 26.8% of the cases. There was no mortality or major morbidity after surgery. The 5-year overall survival was impressive at 52.7%, which is better than the 5-year survival from chemoradiotherapy alone reported in the literature [14]. There was no difference between the carboplatin–paclitaxel or carboplatin–docetaxel arms.

The benefit of addition of radiation to neoadjuvant chemotherapy was further evaluated in a very small randomized clinical trial between neoadjuvant chemotherapy and chemoradiotherapy in patients with N2 disease [24]. A total of 36 patients received cisplatin- and docetaxel-based neoadjuvant chemotherapy and 46 received neoadjvuant chemoradiotherapy, either sequentially or concurrently with chemotherapy. Complete resection after chemotherapy and chemoradiotherapy was achieved in 92 and 94% of the patients, respectively. There was no difference in 90-day mortality between the two groups; however, incidence of postoperative acute respiratory distress syndrome was marginally higher after chemoradiotherapy (13%) as compared with after chemotherapy alone (3%; $p = 0.09$). In the chemotherapy group, pN0 was seen in 33% of samples and 61% of patients had pathological down-staging. After chemoradiotherapy, pN0 was seen in 67% of the patients with 78% of the patients undergoing pathological down-staging. The difference in pathological down-staging between chemotherapy and radiotherapy was significant ($p < 0.01$). The disease-free survival was significantly better in the chemoradiotherapy arm; HR of 0.52 ($p = 0.04$). However, the overall 5-year survival of all patients was 40%, with no significant difference between chemotherapy and radiotherapy arms [24]. This is a very small clinical trial and there is considerable potential for a chance imbalance between the two groups.

Patients with stage III NSCLC are treated with definitive chemoradiotherapy and the role of surgery in these patients is still under exploration. In this regard, neoadjuvant concurrent chemoradiotherapy and surgery were compared with definitive chemoradiotherapy in a large international Phase III clinical trial led by Albain [25]. Patients with stage III (N2) NSCLC were randomized in a 1:1 ratio to concurrent induction chemotherapy (two cycles of cisplatin: 50 mg/m^2 on days 1, 8, 29 and 36; and etoposide: 50 mg/m^2 on days 1–5 and 29–33) plus radiotherapy (45 Gy). If no progression occurred, patients in group 1 underwent resection and those in group 2 continued radiotherapy, uninterrupted, up to 61 Gy. Two additional cycles of cisplatin and etoposide were given in both groups. There was a total of 202 patients in group 1 (chemoradiotherapy plus surgery) and 194 in group 2 (chemoradiotherapy). Progression-free survival was better in group 1 than in group 2; median 12.8 months (5.3–42.2) versus 10.5 months (4.8–20.6; HR: 0.77; 95% CI: 0.62–0.96; $p = 0.017$); for patients with a N0 status at thoracotomy, the median overall survival was 34.4 months. However, there was no difference in overall survival between the two groups. Median overall survival was 23.6 months (interquartile range 9.0 not reached) in group 1 versus 22.2 months (interquartile range 9.4–52.7) in group 2 (HR: 0.87; 95% CI: 0.70–1.10; $p = 0.24$). There was an excess of treatment-related deaths in the patients randomized to chemoradiation plus surgery. A total of 16 (8%) patients died in group 1 from causes not attributable to cancer. Of the 16 deaths, 14 were reported in patients undergoing pneumonectomy, one after lobectomy, and only four (2%) patients died in group 2 from treatment-related causes. Patients that underwent lobectomy had a much better median overall survival compared with the corresponding group of patients with concurrent chemoradiotherapy. The median overall survival for patients with lobectomy was 33.6 months compared with 21.7 months in the chemoradiotherapy arm. Therefore, although this study failed to demonstrate overall survival benefit with addition of surgery, it provided very good evidence in a large Phase III randomized clinical trial that neoadjuvant chemoradiotherapy

followed by surgery can improve overall survival, provided pneumonectomy can be avoided as this procedure resulted in poor surgical outcome.

Neoadjuvant chemoradiotherapy in superior sulcus tumors

Patients with superior sulcus tumors represent a unique subset of locally advanced lung cancer patients. Effectiveness of neoadjuvant chemoradiotherapy was studied in a large clinical trial. In this large intergroup cooperative trial from North America, 110 patients with T3–T4 and N0–N1 superior sulcus tumors received two cycles of cisplatin and etoposide, concurrently, with radiation (45 Gy). Patients with stable or responding disease underwent thoracotomy [26]. All patients received two more cycles of chemotherapy. A total of 95% of the patients completed induction therapy and 80% of the patients underwent thoracotomy. Resections were pathologically complete (R0) in 94% with T3 tumors and 96% with T4 tumors. Pathologic complete response or minimal microscopic disease was seen in 56% of resection samples. In terms of complications, only two patients died postoperatively; however, pulmonary complications were seen in 13.6% of the patients. The 5-year overall survival rate was 44% for all patients and 54% after complete resection, with no difference between T3 and T4 tumors. Disease progression was mostly seen in distant sites.

Pulmonary toxicity from neoadjuvant chemotherapy

One of the concerns associated with using neoadjuvant chemotherapy is its toxicity and the ability of the patient to undergo a subsequent surgical resection. Impact of preoperative chemotherapy on pulmonary function tests (PFTs) in resectable early-stage NSCLC was evaluated in a clinical trial published in *Chest* 2009 [27]. A total of 87 patients underwent three cycles of gemcitabine-based neoadjuvant chemotherapy prior to surgical resection. PFT and dyspnea scores were obtained at baseline and after chemotherapy. Changes in forced vital capacity, forced expiratory volume in 1 s and total lung capacity were not statistically different after chemotherapy. Although 27% of patients in the study had some reduction in PFT results, only two of the 85 eligible patients did not undergo surgery as a result of PFT reduction following chemotherapy. One patient experienced a clinically significant respiratory toxicity (grade 3 dyspnea). The diffusing capacity of the lung for carbon monoxide adjusted for hemoglobin declined by 8% from pre- to post-induction ($p < 0.0001$). Although preoperative neoadjuvant chemotherapy did have an impact on pulmonary functions in this study, especially the diffusing capacity of the lung for carbon monoxide, it did not translate into a significant pulmonary toxicity and it did not prevent patients from undergoing surgical resection.

Future perspective

As discussed previously, patients with early-stage lung cancer (stage II and IIIA) should be treated with surgical resection followed by adjuvant chemotherapy, the current standard of care. Although clinical trials have demonstrated the benefit of neoadjuvant chemotherapy in early-stage lung cancer, the current standard of care remains surgery followed by adjuvant chemotherapy. A possible future clinical trial could compare neoadjuvant versus adjuvant chemotherapy in early-stage lung cancer to see which approach is more feasible, most efficacious and least toxic. A similar trial was carried out previously [11], but most patients in this clinical trial had stage I disease for which no benefit of adjuvant chemotherapy exists. Therefore, in future, such trials should only include patients with stage II or stage IIIA disease.

The role of neoadjuvant chemotherapy needs to be explored further in locally advanced lung cancer, possibly in combination with radiation. Whereas neoadjuvant chemotherapy or chemoradiotherapy followed by surgery is routinely used in locally advanced esophageal [28] and rectal cancers [29], and locally advanced head and neck cancer [30], its use in locally advanced lung cancer remains under investigation.

While conducting future research involving neoadjuvant chemotherapy in locally advanced lung cancer, it is important to distinguish between patients with small N2 disease, and those with bulky N2 and N3 disease. Patients with small N2 disease should be included in clinical trials in which patients are treated with neoadjuvant chemotherapy or chemoradiotherapy followed by surgical resection. One difficulty with using radiotherapy in patients with lung cancer in the neoadjuvant setting is the pulmonary toxicity associated with such an approach [24]. Patients undergoing pneumonectomy have had a worse surgical outcome. Future trials should be designed to limit pulmonary toxicity from radiation and, if possible, avoid penumonectomy.

Patients with bulky N2 and N3 disease should be approached differently. A surgical approach may not be possible in most patients

even after neoadjuvant chemoradiotherapy and these patients are more likely to benefit from definitive chemoradiotherapy.

Most patients with locally advanced lung cancer, especially those with bulky N2 and N3 disease, have occult distant metastasis, which may not be diagnosed by routine staging CT or PET scans at the time of diagnosis. These patients commonly relapse at distant sites after definitive local treatment (65%) [14]. Such patients may benefit from consolidation chemotherapy following definitive chemoradiotherapy. Although a large Phase III clinical trial from the Hoosier Oncology Group did not demonstrate the benefit of consolidation docetaxel [15], a personalized chemotherapy approach, in which consolidation chemotherapy is given based on histology, might be of benefit and needs to be evaluated.

EGF receptor (EGFR) tyrosine kinase inhibitors (TKIs) have shown remarkable activity in a subset of patients with an activating *EGFR* mutation in advanced-stage lung cancer [31]. Response rates of up to 70% have been reported with a single-agent EGFR TKI compared with a response rate of 30–40% with conventional platinum doublet chemotherapy. Few case reports exist in the literature in which EGFR TKIs have been used in the neoadjuvant setting prior to definitive surgery [32,33]. Currently, a clinical trial is open in China evaluating induction erlotinib in stage IIIA (N2) NSCLC patients [102].

In conclusion, there is no well-established role of neoadjuvant chemotherapy in early-stage lung cancer and its role in locally advanced lung cancer, although beneficial, remains investigational.

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Executive summary

Neoadjuvant chemotherapy in early-stage lung cancer

- Early-stage lung cancer is treated with surgery followed by adjuvant chemotherapy.
- A meta-analysis of 34 trials compared chemotherapy followed by surgery with surgery alone and found an absolute increase in survival of 4% at 5 years with a hazard ratio of 0.86 (95% CI: 0.81–0.92; $p < 0.0001$).
- Recent clinical trials evaluating neoadjuvant chemotherapy in early-stage lung cancer have been closed early owing to the clear benefit of adjuvant chemotherapy.

Neoadjuvant chemotherapy in locally advanced lung cancer

- Individuals with locally advanced lung cancers represent a heterogeneous group of patients and are treated with surgery followed by adjuvant chemotherapy or, more often, definitive chemoradiotherapy.
- Neoadjuvant chemotherapy in locally advanced lung cancer has shown mixed results, with some trials showing benefit and others not.
- Two meta-analyses have demonstrated the benefit of neoadjuvant chemotherapy with a hazard ratio of 0.82 (95% CI: 0.69–0.97) and 0.84 (95% CI: 0.77–0.92). However, some of the trials in the meta-analysis had a small sample size.
- A sub-group analysis from one of the meta-analyses shows that neoadjuvant chemotherapy may improve survival in patients with stage III lung cancer with a hazard ratio of 0.84 (95% CI: 0.75–0.95).

Neoadjuvant chemotherapy & radiotherapy in locally advanced lung cancer

- Several small trials have demonstated the benefit of the addition of radiation to neoadjuvant chemotherapy in locally advanced lung cancer.
- A large Phase III clinical trial failed to demonstrate survival advantage with neoadjuvant chemoradiotherapy followed by surgery as opposed to chemoradiotherapy alone. Patients had improved survival if they underwent lobectomy as opposed to pneumonectomy.
- Addition of radiation to chemotherapy in a neoadjuvant setting can cause pulmonary damage with a higher incidence of postoperative acute respiratory distress syndrome as opposed to neoadjuvant chemotherapy alone.

Neoadjuvant chemoradiotherapy in superior sulcus tumors

- Patients with superior sulcus tumors represent a unique subset of patients who are treated with neoadjuvant chemoradiotherapy followed by surgery with a 5-year overall survival of 44%.

Pulmonary toxicity from neoadjuvant chemotherapy

- Neoadjuvant chemotherapy leads to reduction in the diffusing capacity of the lung for carbon monoxide with minor changes in pulmonary function tests, and does not translate into significant pulmonary toxicity or prevent patients from undergoing surgery.

Future perspective

- There is no established role of neoadjuvant chemotherapy in early-stage disease.
- The role of neoadjuvant chemotherapy in locally advanced lung cancer, although beneficial, needs further exploration and currently remains investigational.
- Targeted agents are also being utilized in a neoadjuvant setting in lung cancer.

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