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Resection for Patients Initially Diagnosed with N3 Lung Cancer after Response to Induction Therapy

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Lung cancer is classified as N3 when metastases to the contralateral mediastinal and hilar lymph nodes, the supraclavicular nodes, and the scalene nodes are present at the time of diagnosis. N3 lung tumors have been included in stage IIIB since 1986, when it appeared clear that such locally advanced disease needs to be grouped in a separate stage III category because of the extremely poor prognosis. In the large series reported by Mountain, 5-year survival for N3 patients was 3%.[1] These tumors have always been considered inoperable due to the difficulties in eradicating all the detectable disease that markedly limits the applicability of primary surgery in this setting.

N3 lung cancer has been approached aggressively with initial surgery in a few centers, mainly by Japanese groups.[2,3] The pulmonary resection is carried out through a median sternotomy, and complete bilateral lymphadenectomy is accomplished. The limited survival benefit observed with such an aggressive approach has, however, strongly discouraged the choice of primary operation.

Bimodality protocols of chemotherapy combined with definitive thoracic irradiation represents, at the moment, the standard treatment of care for N3 and all stage IIIB patients.[4–6] Recently, concurrent administration of these two therapeutic options has been recommended because it provides improved survival in comparison to sequential chemoradiotherapy, although it is frequently associated with increased toxicity.[4,7–9] With this combined modality therapy, the expected 5-year survival ranges between 10% and 15%.[4] However, this treatment achieves tumor sterilization in only 5% to 20% of the patients,[10,11] and locoregional failure is almost the rule with a local control of 17% at 1 year in randomized studies.[12] This argument strongly supports the search for an alternative strategy of treatment in the attempt to achieve a more complete oncologic control.

Neoadjuvant chemotherapy or chemoradiotherapy followed by surgical resection has been used in patients with stage IIIA-N2 disease since the end of 1980s, showing significant survival advantage in small randomized studies. In some of these studies, carefully selected IIIB patients have been enrolled and their survival results, in initial experiences, did not differ markedly from the IIIA group.

The analysis of data concerning complex and aggressive therapeutic options including surgery in poor-prognosis groups of patients, such as N3, has to necessarily undergo a meticulous evaluation of the methods employed and, in particular, of the staging and restaging modalities, inclusion criteria, induction protocols, and surgical technique.

15.1. Staging Modalities

Staging modalities should be rigorously evaluated and verified when comparing results by different centers, including heterogeneous protocols. Inaccurate clinical staging invariably limits the significance of reported clinical results. In particular, trials not including surgery usually enroll

patients without positive histological staging. Even in the most recent studies with chemotherapy or radiochemotherapy followed by surgery, pretreatment staging accuracy is often questionable and varies from one investigator to another.

Diagnostic imaging of the mediastinum with purpose of lymph nodal staging before treatment is still most commonly based on computed tomography (CT). The use of dimensional criteria (lymph node size >1 cm) as the sole parameter to assess the presence of nodal metastases strongly limits the efficacy of the technique in this setting. Computed tomography alone has been found to have low sensitivity (56%–63%) and specificity (60%–90%), with an accuracy ranging from 61% to 85% for identification of malignant N2 and N3 lymph nodes.[13–15] The false-negative rate has been registered as high as 30% in several experiences.[16] Moreover, the sensitivity and the accuracy of CT scan for detecting lymph nodal metastases are lower after induction therapy.[17] Therefore, surgical exploration of the mediastinum, principally by means of mediastinoscopy, has often been advocated for histological confirmation of staging.

In experienced hands mediastinoscopy is extremely accurate, showing an average sensitivity of 84%, a specificity of 100%, and a false-negative rate averaging 9% in 10 large series[18–27] published over a 15-year period. Some authors[17] have recently hypothesized that the use of a video-assisted approach (videomediastinoscopy) has contributed an increased efficacy of mediastinoscopy, including after induction therapy. The accuracy of video-assisted mediastinoscopy after neoadjuvant chemotherapy has been reported as high as 91%, with results similar to those observed in patients without preoperative treatment.

Currently employed alternative tools for invasive mediastinal staging of lung cancer, including anterior mediastinotomy, videothoracoscopy, and extended mediastinoscopy, play a lesser role in the preoperative histological diagnosis of N3 disease. Extended cervical mediastinoscopy has been proven an effective technique for sampling enlarged lymph nodes in stations 5 and 6 that are not reachable by conventional mediastinoscopy. Ginsberg[28–30] reported a sensitivity of 69%, a specificity of 100%, and an accuracy of 91% in a series of 300 cases. However, concern about the technical complexity of this approach has limited its use to a few experienced centers and generally for confirmation of N2 disease in left lung cancer. There are sporadic experiences in the literature reporting the adoption of this procedure for staging of N3 disease. Similarly, videothoracoscopy, which has been proposed as an effective method for surgical exploration of the aorto-pulmonary window and the para-aortic lymph nodal station, has achieved a limited application in the diagnosis of the N3 disease. In clinical practice, it has been more frequently used for staging suspected T4 lung cancer. Direct biopsy of the supraclavicular nodes and the scalene nodes can be accomplished without particular technical difficulties, but the presence of tumor in these sites is considered an exclusion criteria in many trials including N3 patients.[6,31–33] More recently, fiber-optic transbronchial needle aspiration, by either cytological or histological needle, has been reported as a safe and effective alternative to mediastinoscopy in suspected N2 and N3 lung cancer.[34–36] Although sensitivity and accuracy of this technique in this setting have been reported as high as 71% and 73%, respectively (84% and 86% for the right paratracheal nodes),[35] these procedures are still not widely performed and only selected centers have reached adequate experience.

All the above-mentioned data have justified a general affirmation of invasive procedures for mediastinal staging. In the literature, almost all phase II trials including N3 patients have employed mediastinoscopy to confirm lymph nodal involvement.[6,9,10,32,33,37]

15.2. Restaging Tools

A number of considerations should be made when analyzing data from different studies administering induction therapy in order to evaluate the appropriateness of the restaging tools employed and the scientific accuracy of the results obtained. First, there is evidence in literature that pathological mediastinal downstaging is one of the most powerful predictors of survival after resection following induction therapy. This has been principally proven in series of N2

patients, but has been also verified in few selected experiences including N3 patients. Second, currently employed imaging methods have shown disappointing efficacy in mediastinal restaging after neoadjuvant treatment. Computed tomography can be very misleading in this setting because the presence of lymph nodes appearing with pathological size (more than 1 cm in diameter) has been proven to be unrelated to the neoplastic disease in up to 40% of patients.[38] This is due to the scarring and inflammatory changes induced by the treatment of the initially neoplastic lymphadenopathy, which may explain the persistence of radiologically anomalous tissue in the site of the previously detected pathologic nodes. Finally, fluorodeoxyglucose (FDG)-positron emission tomography (PET) has shown a significantly lower accuracy in mediastinal staging after induction therapy because chemotherapy and radiotherapy induce reactions in lymph nodes that may lead to increased FDG uptake.[39]

As a consequence, a number of authors have advocated surgical re-exploration of the mediastinum as the only effective means to achieve a proper selection of patients likely to benefit from surgical resection after induction therapy. Repeat mediastinoscopy has been routinely performed in this field only in selected centers with considerable experience.[33,38,40] Despite technical difficulties due to mediastinal fibrosis and peritracheal adhesions, this procedure can be done without increased morbidity and with satisfactory results. Sensitivity, specificity, and accuracy of repeated medistinoscopy after induction treatment have been reported as high as 73% to 75%, 100%, and 80% to 85% in the two larger series in the literature.[38,40] Although slightly lower than that of initial mediastinoscopy, the accuracy of this procedure allows adequate pathological restaging of the mediastinum in lung cancer. The only contrasting experience, in terms of results, is the one published by Pitz.[33] However, the lower diagnostic value of the technique in this series can be explained by the high number of incomplete procedures.

Lardinois[17] has recently investigated the role of videomediastinoscopy in patients submitted to induction therapy without previous exploration of the mediastinum, and who showed radiological response to treatment. Results were compared with those of the same technique in potentially operable patients without preoperative treatment. Safety (0% vs. 4% morbidity) and accuracy (91% vs. 95%) were similar with and without induction therapy. Videomediastinoscopy revealed the presence of N2 or N3 disease in 17% of patients with mediastinal lymph nodes smaller than 1 cm at CT scan after neoadjuvant therapy.

Thoracotomy is hardly acceptable as a staging or restaging method in a setting where the real benefit of surgery is still to be quantified. Therefore, thoracotomy might be employed only after other staging methods proved inconclusive. The introduction of FDG-PET scan has partially modified the diagnostic strategies for the selection of patients to either primary surgery or after induction therapy. In a recent prospective study, the integrated use of FDG-PET with CT has significantly improved the nodal staging accuracy if compared with CT alone, but also with FDG-PET alone.[41]

However, the combination of mediastinoscopy and PET has proved to considerably improve the efficacy of mediastinal staging of lung cancer.[42] In the study from Kernstine,[42] if PET is negative in either N2 or N3 nodes there is little probability of mediastinal disease (1%–8%), but when PET is positive in N2 or N3 sites, the metastatic tumor is not histologically confirmed in 40% to 60% of the cases, so that mediastinoscopy is recommended. Moreover, PET has shown a significantly lower accuracy for mediastinal staging in patients who underwent induction therapy than in patients without preoperative treatment, with a sensitivity of 67% and a specificity of 61%.[39] Among the possible explanation of this phenomenon, it has been hypothesized the release of metabolically active phagocytes and cytokines by nonpathological tissue as a reaction to the treatment, that may lead to increased FDG uptake in the site of original tumor producing false-positive results.

In conclusion, mediastinoscopy has increased accuracy in mediastinal staging compared with noninvasive methods, and is also effective in clinical re-evaluation after preoperative treatment. However, the increased technical complexity of re-operative mediastinoscopy often discourages surgeons to routinely repeat this procedure and only few trials in the literature[6,33] report its inclusion in the postinduction restaging.

15.3. Role of Surgery

15.3.1. Therapeutic Protocols, Surgical Techniques

There is general consensus about the principle that lung cancer cannot be cured unless all detectable disease is eradicated. All the integrated strategies of cure proposed in the last decades for patients with unresectable lung cancer, such as stage IIIB disease, have invariably failed in achieving adequate tumor sterilization. In addition, the disappointing results reported when surgery alone is employed suggest that the efficacy of this option should be reconsidered with a different strategy.

Selected N3 patients have been included in a number of phase II studies exploring the potential benefits of surgery after neoadjuvant treatment in stage IIIB. Data available in the literature usually do not report separate analysis for N3 and T4 patients, so that it is difficult to acquire specific prognostic indications for each of these subgroups. Moreover, published experiences in this field generally differ for restaging methods employed, because pathological re-evaluation of lymph nodal status is performed only in a few series, and for dishomogeneity of surgical technique, because the exploration of the contralateral mediastinum is only rarely carried out.

The Southwest Oncology Group has reported an induction chemoradiotherapy trial (SWOG 8805) that included a large group of patients with stage IIIB disease.[10] An effort was made to adhere to strict staging criteria prior to inclusion in the study: all N3 patients had histological confirmation by means of mediastinoscopy. The induction treatment consisted of concurrent chemotherapy and radiotherapy. Two cycles of cisplatin (50 mg/m^2) were administered concurrently with 45 Gy radiotherapy. Major toxicity was registered in 4% of patients. Fourteen of 27 patients with N3 disease (52%) underwent surgery after response to therapy. Repeat mediastinoscopy was not performed in the postinduction selection for thoracotomy. N3 patients were approached by standard thoracotomy and no attempt was made to resect the previously involved contralateral or supraclavicular lymph nodes. The decision apparently was based on the assumption that surgery was regarded only as an adjuvant for primary tumor control.

The last update of SWOG 8805 was issued in 1999[37] with 6-year survival data: the overall (all N3 and T4) survival was 22% with definitively more favorable prognosis (6-year survival, 49%) in the substage of T4 without mediastinal lymphadenectomy (N0-1). N2-3 patients showed markedly improved prognosis (6-year survival, 33%) when pathological downstaging to N0 was present if compared with patients presenting with unmodified lymph nodal status (6-year survival, 11%). Sites of relapses resulting in death were predominantly extrathoracic. Brain metastases were observed in 25 of 51 patients, being the sole site of recurrence in 18.

A second important phase II trial appearing in 1999 by Stamatis and colleagues[6] employed three cycles of cisplatin (60 mg/m^2) and etoposide (150 mg/m^2) followed by one cycle of concurrent hyperfractionated accelerated radiotherapy (45 Gy) and chemotherapy with the same agents at lower doses. Among the N3 histologically proven patients, only those[32] without supraclavicular or scalene adenopathy were enrolled. The authors' purpose was to identify stage IIIB subgroup with better long-term prognosis. Repeat mediastinoscopy was performed after induction therapy and only patients with negative results proceeded to surgery. Major overall toxicity after the induction protocol was seen in 19.6% of patients with a 1.7% mortality rate. The complete resection rate was 48%.

As in the SWOG study, Stamatis and coworkers approached these patients by standard thoracotomy without any surgical exploration of the contralateral mediastinum. However, all former N3 patients had negative mediastinoscopy prior to surgery. The complex induction treatment protocol may have influenced the high postoperative complications rate (47%) observed, but it didn't strongly modify surgical mortality (2.9%). Survival rate of N3 patients at 5 years after operation was 28%. Long-term survival appeared possible in originally N3 patients with limited extension of the primary tumor (T1-2). As in the SWOG study, in the first part of this experience, a significant number of early brain metastases was noted. The addition of prophylactic cranial irradiation to the protocol reduced the incidence of cerebral metastases from 46% to 9%.

Another German trial[43] was published in 1999 including 15 N3 patients submitted to a complex and aggressive regimen. Chemotherapy (two cycles of ifosfamide, carboplatin, and etoposide) and subsequent radiotherapy (45Gy, twice daily 1.5Gy) concurrent with chemotherapy (carboplatin and vindesine) were administered. The intensive chemoradiotherapy regimen in this study significantly increased tumor regression rate (41% after chemotherapy alone and 69% after the complete chemoradiotherapy course), but critical toxicity was registered with a 9% mortality rate. Results for the sole N3 group were not reported in detail, but the overall median survival after surgery for stage IIIB (20 patients) of 17 months did not show significant differences with that of stage IIIA (25 months). Patients experiencing a 90% degree of pathologic tumor regression were most likely to achieve long-term survival.

A phase II study by Grunenwald and associates[32] has reported some innovative aspects, especially for the surgical approach to N3 disease. Induction regimen included two cycles of cisplatin, 5-fluoruracil (5-FU), and vinblastine combined with 42Gy of concurrent accelerated twice-daily radiotherapy. Nineteen mediastinoscopy proven N3 patients were enrolled. Complete disappearance of mediastinal lymph node involvement (N2/N3) was observed in 30% of patients. The operation was performed through a median sternotomy, and a complete bilateral mediastinal lymphadenectomy was carried out. Pneumonectomy was performed in 60% (18/29) of the patients with systematic bronchial stump protection by the omentum harvested using a small downwards extension of the midline skin incision. The reported complication rate was 24%, there was a 7% mortality rate, and the mean postoperative in-hospital stay was 20 days. Survival at 5 years was 17% for all N3 patients, including nonsurgically treated patients. However, significant survival improvement was observed when considering, in the whole study population (all stage IIIB), the partial responders with postinduction N0-1 status who were submitted to surgery (47% at 5 years). In this series, all 4 patients with histological complete response to treatment were not alive at the time of publication, suggesting also that adequate locoregional control may be not sufficient in achieving complete tumor sterilization.

The Massachusetts General Hospital group[44] focused on another aspect of induction therapy: the search of the best way of delivering radiotherapy. In association with cisplatin, vinblastine, and 5-FU, preoperative radiotherapy was administered with two levels of radiation doses: 45Gy in 25 fractions for 5 weeks to the initial volume (gross tumor plus adjacent lymph node–bearing region) and 44 to 60Gy to the gross tumor including involved lymph nodes by using boost radiation for a dose of 9 to 15Gy during chemotherapy. This algorithm was employed in 20 N3 and 5 T4 patients, 13 of whom (52%) underwent resection. No mention was made about surgical exploration of the contralateral mediastinum. The reported 3-year survival reached 54%.

Recently, a Dutch prospective phase II multicenter trial[33] has appeared investigating the role of surgery as a part of combined modality treatment in association with chemotherapy. Surgery plus chemotherapy was compared with radiotherapy plus chemotherapy, and the diagnostic value of postinduction repeated mediastinoscopy was analyzed. Histologically proven N3 patients were included in an overall study population of 41 patients and submitted to three courses of neoadjuvant gemcitabine/cisplatin chemotherapy. Four patients stopped the treatment after the first two cycles. Forty-eight percent of the N3 patients underwent resection after response to therapy. Survival in the whole study population did not show a significant advantage with a 15% survival rate at 3 years. Median survival of patients experiencing partial or complete response who were submitted to surgery was 21.5 months. There were equal incidences of local and distant recurrences as cause of death. Postinduction repeat mediastinoscopy proved to be an ineffective restaging tool because of the high number of incomplete procedures (40%) and the false-negative rate (28.6%).

Other interesting studies have dealt with the issue of induction therapy in stage IIIB[9,31,45] in the last years, but each of them includes a limited number of N3 surgically treated patients, so that data emerging by these experiences do not still provide meaningful indications in this setting. The results of phase II trials including operated N3 patients after induction therapy are reported in Table 15.1.

TABLE 15.1. Phase II trials of induction therapy plus surgery including N3 NSCLC patients.

Reference	Patients (Overall)	N3 Patients	Inclusion cirterla	Induction therapy	Response rate	Resection rate	Complete resection	Derioperative mortality	Operative mortality	Survival (overall IIIB)	N3 survival
Choi[45]	25	16	N3 T4	Cisplatin + 5-FU + velban + RT (60 Gy)	65%	56%	52%	–	–	61% (2 year)	–
Rice[46]	45 (10 IIIB)	8	N2, N3 T4 (except pleural effusion)	Cisplatin + paclitaxel + RT (30 Gy)	53%	89%[a]	71%	20%	5%	17% (2 year)	–
Stamatis[6]	58	32	Medlastinal N3 T4	(Cisplatin + VP-16) × 3 + (Cisplatin + VP-16) × 1 + RT 45 Gy)	61%	59%	48%	47%	5.8% (5-sp)	26% (5 year) C.R.: 43%	28% (5 year)
SWOG[10]	51	27	N3 T4 (except pleural effusion)	(Cisplatin + VP-16) × 2 + RT (45 Gy)	78%	63%	52% (N3)	26%	5.2%	22% (8 year)	–
Thomas[45]	54 (29 IIIB)	15	N2, N3 T4	Ifost + carbopl. + VP-16 × 3 + (Carb + Vindesin) + 45 Gy RT	69%	74%[a]	63%	17.5%	7.5%	26% (3 year) 17 m (median)	–
Grunenwald[32]	40	19	Medlastinal N3 T4	(Cisplatin + 5-FU + Vinblastine) × 2 + RT (42 Gy)	73%	58%	50%	24%	7%	Res: 28% C.R.: 35%	17% (5 sp)
Pltz[33]	41	21	N3 T4	(Cisplatin + Gemcitabine) × 3	88%	50%	25%	30%	5%	15% (3 year) Res: 21.5 m (median)	Res N2-3: 17.5 m (median)
Ichinose[9]	27	7	N3 T4	LFT + Cisplatin + RT (40 Gy)	93%	81%	77%	36%	4%	58% (3 year) Res: 67% (3 year)	–

Abbreviations: C.R., completely resected; Res: responders.
[a]IIIA and IIIB.

Because investigation in this field is currently active, progressive adjustments and refinements have been proposed in the choice of the most effective drugs and the best way of delivering radiotherapy. Therefore, the optimal induction regimen has yet to be identified. Most of the published phase II trials utilized second generation chemotherapy generally based on cisplatin, a vinca alkaloid, and etoposide. Meta-analysis have indicated that the chance of survival increases when a platinum-based regimen is used.[46,47]

15.3.2. New Multimodality Regimens

A number of new agents, tested in clinical trials not including surgical resection, more recently have been introduced in neoadjuvant protocols. In particular, paclitaxel has shown a potent radiosensitizer effect. Gemcitabine, an antimetabolite that functions as an inhibitor of ribonucleoside reductase, has been shown to yield response rates of 20% to 30% when used as a single agent and of 58% to 60% when employed in combination with cisplatin.[5] A synergistic anti-tumor activity of the cisplatin has been shown also in combination with other drugs, such as 5-FU, with a response rate up to 74%, although 5-FU alone is thought to be inactive against non-small cell lung cancer (NSCLC).[31]

Concerning the choice of the best way of administering irradiation, indications have to be determined by phase III trials not including surgery. There are still no convincing data supporting the clinical benefits of altered fractionation modalities, such as hyperfractionated (two or more fractions daily) or continuous hyperfractionated accelerated radiotherapy (CHART), in combination with chemotherapy if compared with standard radiotherapy.[4,48] There is only one phase III trial showing superior results for CHART without chemotherapy with respect to standard radiotherapy, but the logistics of three treatments daily have not proven to be acceptable.[49,50]

Results of phase II trials have pointed out that the administration of multidrug chemotherapy and multimodality protocols, including radiotherapy preoperatively, is able to achieve higher clinical and pathological response rates.[6,32,33] Response rates (reported for all stage IIIB patients) seem to be similar in almost all the studies reported, and range between 61% and 78%. The 93% rate registered by Ichinose and collegues[9] is justified, as explained by the authors, by the more restrictive inclusion criteria adopted. The complete response rate for N3 is specifically mentioned only in the SWOG study (52%). The complete histological response generally varies between 10 % and 15%; however, in the Stamatis trial,[6] based on a heavy chemoradioterapy regimen, the complete histological response rate increased up to 30%.

15.3.3. Effects of Nodal Downstaging

Maximal downstaging after induction therapy has been advocated in main experiences as the strongest predictor of survival in N3 and all stage IIIB patients undergoing surgical resection. Several authors have reported, as expected, a prominent prognostic significance of lymph node status after induction treatment. In the study by Choi and collegues,[51] the degree of lymph node downstaging showed a direct relation to survival benefit because the 5-year survivals were 79%, 42%, and 18% for postoperative tumor stages 0/I, II, and III, respectively. In the SWOG experience,[10] the most significant predictor of long-term survival after thoracotomy was the absence of tumor in the mediastinal nodes (3-year survival, 44% vs. 18%). Stamatis[6] reported a 4-year survival of 38% and 15% in postinduction N0/N1 and N2/N3 patients, respectively. Also in the French study,[32] postinduction completely resected N0-1 patients showed a 5-year survival of 42%, while postinduction N2-3 patients who underwent complete resection reached only a 12% survival rate at 5 years.

Altogether, all these prognostic evidences support the principle that admission to surgery after neoadjuvant therapy in advanced stage lung cancer, such as N3, has to be strictly limited to those patients who show a major clinical response. In the German trial,[6] only those N3 patients were operated in whom initially involved nodes were without evidence of residual cancer at repeat mediastinoscopy or if not more than one initially involved ipsilateral node remained positive.

15.3.4. Effects of Tumor Sterilization

The impact on prognosis of residual viable neoplastic cells in the primary tumor has not been completely clarified. In German Lung Cancer Cooperative Group study,[43] tumor regression of more than 90% appeared related to a significantly improved survival in the completely resected (R0) group of patients (3-year survival, 56% vs. 11%). Conversely, in the other German trial,[6,52] no difference in survival was found between resected patients assessed to have pathological complete response versus those with persistent viable tumor. It is still object of controversy whether pathological complete disappearence of tumor at the primary site has to be interpretated also as a predictor of responsiveness of distant micrometastases, determining an impact on long-term survival. In some authors' opinion,[6,52] especially when radiotherapy is added to preoperative chemotherapy, pathological complete regression at thoracotomy has only to be seen as the effect of the aggressive local treatment on the primary tumor and may no longer indicate superior efficacy in systemic control of the disease.

15.3.5. Treatment-related Morbidity and Mortality

Increasing complexity and aggressiveness of the induction regimens with the aim of maximal loco-regional control may have played a role in treatment-related morbidity. Although overall toxicity is generally acceptable with rates ranging between 4%[10,37] and 10%,[33] in some heavy multimodality regimens this incidence has proven definitely higher. In the Stamatis trial,[6] 19% of the patients had major toxicity that precluded further treatment and 9% refused to follow the protocol.

Furthermore, in many reports, the use of neoadjuvant therapies has produced increased postoperative complications and mortality rates. High rates of non–cancer-related deaths (20%–26%) have been reported by Grunenwald,[32] Albain,[10] and Eberhardt,[52] often associated with a critical incidence of acute distress syndrome or pneumonitis, if compared with standard resections without preoperative treatment. In particular, when also radiotherapy is administered, it has been frequently documented as a more evident impact on surgical morbidity, often associated with considerable intraoperative technical problems. Several studies have suggested that preoperative chemoradiotherapy may strongly promote bronchial stump insufficiency with a consequent increased incidence of broncho-pleural fistulas up to 23%.[53] Postoperative mortality in Fowler's experience[53] has exceeded 20%.

Pneumonectomy, and especially right-side pneumonectomy, have produced more significant worsening of morbidity and mortality rates in several postinduction surgical series.[53,54] Moreover, also the occurence of a bronchial stump dehiscence has been more frequently observed after right pneumonectomy.[53] A significant reduction of broncho-pleural fistulas rates has been shown in some recent issues[32,55] performing bronchial reinforcement by viable tissue, principally with muscle or omentum. However, in other experiences[56,57] the appearence of fistulas in spite of bronchial stump coverage, especially when intercostal muscle is used, provides no complete evidence of efficacy to these procedures after induction therapy. Mainly when radiotherapy is performed, the tissues employed for the flap may be deteriorated by the oncological therapy, especially if included in the irradiation field. In some authors' opinion,[6] the introduction of twice-daily radiotherapy is a possible mean to shorten radiation duration, and, thus, leads to reduced development of fibrosis at the moment of surgery.

The strong impact on toxicity and surgical complication of the aggressive currently employed three modality treatments has indicated that enrolment in these protocols should be strictly limited to patients with good performance status (0–1) and minimal weight loss.

15.3.6. Impact of Extended Resections

It is now evident that major clinical response to therapy is mandatory to select patients with original N3 disease suitable for surgical resection. However, the slender data present in literature have still not clarified whether, after an intensive preoperative downstaging, the extension of the surgical resection can be confined to the primary lung tumor and the ipsilateral mediastinum or has to include the contralateral mediastinal nodes.

In the Grunenwald trial,[32] the authors advocated the need for extended procedures, including routine bilateral lymphadenectomy, for postinduction surgery. This choice was based on the principle that all the originally involved tissue should be removed despite restaging that showed complete disappearance of disease in mediastinal lymph nodes. In the Essen group experience,[6] employement of invasive mediastinal restaging by repeat mediastinoscopy was indicated as an effective method to avoid such extended resections. In the latter study, the low mediastinal relapse pattern observed in initially N3 patients, proved, in the authors' opinion, that standard procedures without bilateral lymphadenectomy may be sufficient after negative preoperative rebiopsy of the contralateral nodes.

Pneumonectomy is reported to be necessary to achieve complete tumor clearance in a high rate of patients, exceeding 40% in several series,[6,9,32,43] and this requirement further increases the risk for morbidity. In our previous experience,[58] we have shown that operations such as bronchovascular reconstruction not only are technically feasible after induction therapy, but also carry a lower morbidity and comparable long-term survival when compared with pneumonectomy in this setting. Complex surgical interventions, including sleeve resections or extended resections to the carina, the superior vena cava, the left atrium, the esophagus, and the vertebral bodies, have been performed in many of the series reported in this chapter[6,9,32,43] with a high incidence ranging from 40% to 88%, and the related surgical mortality did not show a significant worsening.

15.4. Conclusions

The results of the phase II studies suggest that therapeutic nihilism when confronted by N3 and stage IIIB NSCLC may partially be overcome. Investigators have to consider that, in selected series, surgery associated with currently available chemoradiotherapy may prove able to cure a meaningful rate of patients, which is a better rate than that obtained without surgery (level of evidence 2-; grade of recommendation D). This could be partially explained by the more restrictive selection criteria applied by these aggressive protocols. Because the long-term survival improvement may average about 10% if compared with historical controls without surgery, future comparative analyses are awaited to assess whether this advantage could be confirmed in a randomized study.

Resection in combination with currently available chemoradiotherapy may prove able to cure a meaningful number of patients with N3 NSCLC, which is a better rate than that obtained without surgery (level of evidence 2–; grade of recommendation D).

Although prospective, randomized trials have not yet reported and surgery cannot be recommended at the moment as a standard of care, some convincing indications can be acquired by the published experiences, and the data actually available may help to define precise guidelines for future phase III trials. The first evidence is that accurate preoperative staging and restaging is mandatory. Direct biopsy procedures, mainly by means of mediastinoscopy, have proved superior to all other conventional diagnostic methods in assessing the presence of N2/3 disease, both in the staging and in the restaging setting. Therefore, at the present time, invasive preoperative explorations can be recommended in order to achieve a more accurate selection of patients for such heavy therapeutic protocols (level of evidence 2++; grade of recommendation B). The second is that in well-identified subgroups, such as completely resected patients showing a mediastinal downstaging to N0-1 status, the benefits of surgery are more significant (level of evidence 2+; grade of recommendation C).

Invasive preoperative explorations are recommended in order to achieve a more accurate selection of patients for resection after induction therapy (level of evidence 2++; grade of recommendation B).

In well-identified subgroups, such as patients with mediastinal downstaging to N0-1 status, the benefits of surgery are more significant (level of evidence 2+; grade of recommendation C).

Multi-institutional studies appear necessary to confirm in larger series the clinical evidences observed. Moreover, there are other questions that still remain open: they regard the need of extending the surgical resection to the contralateral mediastinum after high response to treatment, and the choice of the most appropriate induction regimen. Both questions can only be clarified by further controlled studies.

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