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# Neoadjuvant Radiotherapy/Chemoradiotherapy in Locally Advanced Non-Small Cell Lung Cancer

Deniz Yalman

Department of Radiation Oncology, Ege University Faculty of Medicine, İzmir, Turkey

Locally advanced non-small cell lung cancer (NSCLC) consists of a heterogeneous group of patients, and the optimal treatment is still controversial. The current standard of care is concurrent chemoradiotherapy. The prognosis is still poor, with high rates of local and distant failure despite multimodality treatment. One of the efforts to improve outcomes in these patients is to use neoadjuvant treatment to improve resectability, and downstaging the nodal disease, which has a clear impact on prognosis. Radiotherapy as the sole neoadjuvant modality has been used historically without any survival benefit, but with increased toxicity. After the demonstrating a survival benefit by combining radiotherapy and chemotherapy, phase II studies were started to determine the neoadjuvant administration of these two modalities together. Although the results of these studies revealed a heterogeneous postinduction pathologic complete response, tumor and nodal downstaging can be achieved at the cost of a slightly higher morbidity and mortality. Subsequent phase III trials also failed to show a survival benefit to surgery, but indicated that there may be a subset of patients with locally advanced disease who can benefit from resection unless pneumonectomy is not provided. In order to increase the efficacy of radiotherapy, hyperfractionated-accelerated schedules have been used with promising complete pathologic response rates, which might improve prognosis. Recently, studies applying high radiotherapy doses in the neoadjuvant setting demonstrated the safety of resection after radiotherapy, with high nodal clearance rates and encouraging long-term survival results.

In conclusion, neoadjuvant treatment of locally advanced NSCLC is one of the most challenging issues in the treatment of this disease, but it can be offered to appropriately selected patients, and should be done by a multidisciplinary team. Individual risk profiles, definite role of radiotherapy with optimal timing, and dose need to be clarified by carefully designed clinical trials.

**Keywords:** Locally advanced non-small cell lung cancer, neoadjuvant chemoradiotherapy, neoadjuvant radiotherapy

Approximately one third of non-small cell lung cancer (NSCLC) patients present with locally advanced disease (stages IIIA/IIIB), and since this is an extremely heterogeneous group, the optimal treatment is still controversial. The current standard of care in these patients is concurrent chemoradiotherapy. However, the prognosis is poor, with high rates of local and distant failure, and five-year overall survival (OS) rates ranging between 15% and 25% (1). In a minority of selected patients, one approach that has improved outcomes is the use of a combination of neoadjuvant chemotherapy (CT), radiotherapy (RT), and surgery. The aims of neoadjuvant treatment are to improve resectability by shrinking the tumor,

Address for Correspondence: Dr. Deniz Yalman, Department of Radiation Oncology, Ege University Faculty of Medicine, İzmir, Turkey
Phone: +90 532 570 52 62 e-mail: yalman.deniz@gmail.com
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to downstage nodal disease, to sterilise micrometastases, to enhance local control by removal of the residual tumor and nodal disease, and to improve the delivery of CT and RT to the intended doses. The disadvantages are the negative impact of treatment on patient's performance status, the technically challenging surgery after radiotherapy, and the increased rate of postoperative complications. Several groups have investigated various combinations of RT, CT, and surgery.

## NEOADJUVANT RADIOTHERAPY

Historically, use of radiation therapy as the sole induction modality dates back to 1950's before the existence of effective chemotherapeutics for NSCLC. Pathologic complete response (pCR) rates were reported between 27-46% of patients (2, 3). A collaborative randomised study reported no survival difference between the preoperative RT+surgery and the surgery group, with five-year OS rates of 14% and 16%, respectively (4). Postoperative complications were more frequent in the irradiated group without affecting survival.

A study from the Lung Cancer Study Group (LCSG 881) on 67 randomised patients with pathologic stage III disease who received either preoperative RT or preoperative CT (5) reported disappointing results, with only one patient in each group having a pCR, and a median survival for the entire group was 12 months. In a similar randomised trial from the Cancer and Leukemia Group B (CALGB 9134), which was closed early because of the poor accrual the rates of overall and complete surgical resection, nodal downstaging, failure-free, and OS rates did not differ between the preoperative CT or RT arms (6). Based on these results, neoadjuvant RT as the sole induction modality is not recommended in locally advanced NSCLC due to the lack of survival benefit, increased toxicity, and poor patient compliance.

## NEOADJUVANT RADIOTHERAPY WITH CHEMOTHERAPY

Demonstration of a survival benefit by adding CT to RT for inoperable NSCLC aroused interest in neoadjuvant treatment with RT and CT instead of using either modality alone. The early phase II studies of cisplatin-based CT with RT contained a small number of patients (ranging from 39 to 41) with heterogeneous disease volume (7, 8). In the LCSG 831 trial, the response rate was 51% following induction treatment (7). Complete resection was accomplished in 33% and the median survival was 11 months, with a two-year survival of 8%. Skarin et al. (8) reported an objective disease regression rate of 72% in 41 patients with marginally resectable stage III disease. Surgery was carried out in 90% with a resection rate of all gross disease in 97%. Relapse occurred in 61% of the resected patients. The median survival for all patients was 32 months, with three-year survival rate of 31%.

After the 1990's, second-generation phase II studies utilising concurrent cisplatin based chemoradiotherapy (CRT) before surgery were performed (9-13). These studies varied in patient population, stage subsets, total RT dose and schedule (30–59.4 Gy, conventional-split course), and treatment prescribed after surgery (none-CT±RT). The Southwest Oncology Group (SWOG) 8805, LCSG 852, and CALGB I trials required pathologic proof of N2 disease (9, 12, 13). Rush-Presbyterian and CALGB I studies included T3N0-1 disease, which has a better prognosis (10, 12).

Among these phase II studies, SWOG 8805 was unique regarding the number of patients included (126 eligible patients with pathologically documented T1-4N2-3 disease) (9). Mediastinal downstaging was the strongest prognostic factor for survival (three-year OS rates of 44% and 18% for pN0 and pN2 diseases, respectively). Treatment-related mortality was 10%.

Although the results of these phase II CRT trials cannot be compared directly, one can conclude that this approach is safe and feasible despite slightly higher postoperative morbidity and mortality. Postinduction pCR, nodal downstaging, and T3-4 N0-1 disease are favorable predictors of outcome.

The results of SWOG 8805 led to a phase III trial to determine whether resection resulted in a significant improvement in survival over definitive CRT alone. The largest trial to date testing the role of surgery after neoadjuvant CRT is the North American Intergroup trial 0139 (INT 0139) (14). Four-hundred-twenty-nine patients with T1-3pN2M0 NSCLC were randomly assigned to two cycles of induction CT concurrent with RT, and then to surgery (group 1) or to definitive RT (group 2) if no progression after induction CRT. Both arms received two cycles of consolidation CT. Of the 396 patients (92%) that were eligible for the analysis, 202 were assigned to group 1 and 194 to group 2. One-hundred-sixty-four patients (81%) in group 1 underwent thoracotomy, and 55% of the patients in group 1 and 74% of those in group 2 completed consolidation CT ($p<0.0001$). OS rates were not improved in group 1 *versus* group 2 (median 23.6 months *versus* 22.2 months). The OS rates by postinduction pathologic stage according to N status was longer for patients with T (any) N0 disease (five-year survival rates were 41%, 24%, and 8% for N0, N1-3, or unknown and no surgical resection respectively; $p<0.0001$). Local-only relapses were fewer in group 1 (10% *versus* 22%). Progression-free survival was in favor of the surgical arm (median 12.8 months *versus* 10.5 months, five-year 22% *versus* 11%). Treatment related deaths were more common in group 1 (8% *versus* 2%). In an

**TABLE 1.** Neoadjuvant chemoradiotherapy trials

| Authors | Phase | No. of patients | Stage | Treatment schema | Resection rate (%) | pCR (%) | Nodal downstaging (%) | Overall survival |
|---|---|---|---|---|---|---|---|---|
| Faber et al.[10] (1989) (Rush-Presbyterian) | II | 85 | IIIA/B | CT (PF or PE)+40 Gy split-course RT | 71 | 20 | 26 | Median 22 mts |
| Strauss et al.[12] (1992) (CALGB I) | II | 41 | IIIA/B 80%-N2 | CT (PVF)+30 Gy RT Postoperative CT (PVF)+30 Gy RT | 61 | 16 | - | 58%-1 yr Median 15.5 mts |
| Weiden et al.[13] (1994) (LCSG 852) | II | 85 | IIIA/B | CT (PF)+30 Gy RT | 52 | 9 | - | Median 13 mts |
| Albain et al.[9] (1995) (SWOG 8805) | II | 126 | IIIA/B (75/51) | CT (PE)+45 Gy RT Postoperative CT (PE)+ 14 Gy RT | 85 IIIA (N2) 80 IIIB | 21 | 53 | 27%-3 yrs IIIA 24%-3 yrs IIIB |
| Law et al.[11] (2001) | II | 42 | IIIA/B | CT (PE)+59.4 Gy RT Postoperative CT (PE) | 74 | 21 | 59 | 49.9%-5 yrs |
| Albain et al.[14] (2009) (INT 0139) | III | 429 | IIIA | Arm I (202 pts): CT (PE)+45 Gy RT → Surgery+CT Arm II (194 pts): CT (PE)+45 Gy RT →RT continued to 61 Gy+CT | 76 (155/202) | 14 | 41 (N0) | Arm I: Median 23.6 mts, 27%-5 yrs Arm II: Median 22.2 mts, 20%-5 yrs |

CT: chemotherapy; RT: radiotherapy; CRT: chemoradiotherapy; P: cisplatin; V: vinblastine; F: 5-fluorouracil; E: etoposide

exploratory analysis, OS rates were improved for patients who underwent lobectomy as compared with the rate in the matched definitive CRT group (median survival 33.6 months *versus* 21.7 months, five-year 36% *versus* 18%; p=0.002). OS rates for the pneumonectomy patients were not significantly worse than those for the matched cohort in group 2 (median survival 18.9 months *versus* 29.4 months; five-years 22% *versus* 24%). The authors stated that the absence of any survival benefit with surgery might relate to the high death rate after pneumonectomy, and the decision for trimodality therapy must be made with caution if pneumonectomy is considered. The results of these neoadjuvant CRT trials are summarised in Table 1.

Koshy et al. (15) evaluated the data from the National Cancer Database to examine whether neoadjuvant CRT was associated with improved survival among patients with Stage IIIA (N2) disease. There were 11,242 eligible patients with a median follow-up of 11.8 months. The patients were placed into five groups according to the treatment they received: neoadjuvant CRT+lobectomy (4.9%), neoadjuvant CRT+pneumonectomy (1.7%), lobectomy+adjuvant treatment (4.5%), pneumonectomy+adjuvant treatment (1.1%), or CRT (86.3%). Five-year OS rates according to treatment groups were 33.5%, 20.7%, 20.3%, 13.35%, and 10.9%, respectively, in favor of the neoadjuvant CRT+lobectomy group (p<0.0001). The five-year OS rate of this subset is comparable to the five-year OS rate of the same subset of the INT 0139 study (33.5% and 36%, respectively). The five-year OS rates of the complete pathologic nodal responders were also similar among the two studies (40% and 41%, respectively).

## NEOADJUVANT HYPERFRACTIONATED RADIOTHERAPY WITH CHEMOTHERAPY

In order to counteract tumor cell repopulation and to give higher biologically equivalent doses without increasing the late effects, accelerated or hyperfractionated neoadjuvant RT concurrent with CT was tested in phase II and, subsequently, phase III trials (Table 2). In a trial from the Massachusetts General Hospital (MGH), the resection rate was 93% after split-course hyperfractionated RT concurrent with cisplatin-based CT in biopsy-proven stage IIIA (N2) patients (16). Treatment-related mortality rate was 7%. The OS rates at two, three, and five years were 66%, 37%, and 37%, respectively. The degree of tumor downstaging was related with improved survival. Nodal status and complete resection were independent prognostic factors for survival (p=0.04 and 0.02, respectively).

The West German Cancer Center (WGCC) study reported a complete resection rate of 53% and pCR of 26% after three cycles of CT followed by concurrent CT with hyperfractionated RT (17). The Four-year survival rates for IIIA, IIIB, and R0 patients were 31%, 26%, and 46%, respectively. Of the 50 patients who were tumour-free, 18 (36%) have relapsed, mainly at distant sites.

**TABLE 2.** Studies of neoadjuvant hyperfractionated radiotherapy with chemotherapy

| Authors | Phase | No. of patients | Stage | Treatment schema | Resection rate (%) | pCR (%) | Nodal downstaging (%) | Overall survival |
|---|---|---|---|---|---|---|---|---|
| Choi et al.[16] (1997) (MGH) | II | 42 | IIIA (N2) | CT (PVF)+45 Gy/1.5 Gy bid, split-course RT Postoperative CT (PVF)+ 12-18 Gy/1.5 Gy bid RT | 93 | 9.5 | 67 | 37%-5 yrs |
| Eberhardt et al.[17] (1998) (WGCC) | II | 94 | IIIA/B (52/42) | Induction CT (PE) → 45 Gy/1.5 Gy bid RT+CT (PE) | 66 | 26 | - | 28%-4 yrs |
| Thomas et al.[18] (1999) (GLCCG) | II | 54 | IIIA/B (25/29) | Induction CT (ICE) → 45 Gy/1.5 Gy bid RT+CT (CVd) | 74 | 50 (tumor regression >50%) | - | 3 yrs 56% for R0 resection; 35% for IIIA; 26% for IIIB |
| De Camp et al.[19] (2003) (Cleveland Clinic) | II | 105 | IIIA/B (78/27) | 30 Gy/1.5 Gy bid RT+CT (PPx) Postoperative CT+RT | 79 | 62 (partial response) | 35% pN2 30% pN3 | 32%-5 yrs |
| Thomas et al.[20] (2008) (GLCCG) | III | 524 | IIIA/B (175/349) | Arm I (264 pts) Induction CT (PE) → 45 Gy/1.5 Gy bid RT+CT (CVd)→ Surgery Arm II (260 pts) Induction CT (PE) → Surgery→ 54 Gy/1.8 Gy RT | Arm I 54 Arm II 59 | Arm I 60 Arm II 20 (p<0,0001) | Arm I 46 Arm II 29 (p=0.02) | Arm I 39%-5 yrs all pts 45% R0 resection Arm II 31% -5 yrs all pts 42% R0 resection (p=0.82) |
| Eberhardt et al.[21] (2013) (CISTAXOL) | II | 64 | IIIA/B 25/29 | Induction CT (PPx) → 45 Gy/1.5 Gy bid RT+CT (PE) | 56 | 44 | - | 30.2%-5 yrs 26%-10 yrs |
| Eberhardt et al.[22] (2013) (ESPATUE) | III | 246 | IIIA/B 155/91 | Induction CT (PPx) → 45 Gy/1.5 Gy bid RT+CT (PVin) to surgery (Arm A-81 pts) or CRT (Arm B-80 pts) | 81-R0 resection | - | - | 44.2%-5 yrs Arm A 40.6%-5 yrs Arm B (p=0.31) |

CT: chemotherapy; RT: radiotherapy; CRT: chemoradiotherapy; P: cisplatin; V: vinblastine; F: 5-fluorouracil; E: etoposide; I: ifosfomide; C: carboplatin; Vd: vindesine; Px: paclitaxel; Vin: vinorelbine

The German Lung Cancer Cooperative Group (GLCCG) reported an R0 resection rate of 63% after two cycles of induction CT, and subsequent hyperfractionated RT concurrent with CT (18). Tumor regression more than 90% was achieved in 50%, and it was an independent predictor of long-term survival. The mortality rate was 9%. Survival rates at three-year were 35%, 26%, and 56% for patients with stage IIIA disease, stage IIIB disease, and R0 resections with tumor regression more than 90%.

De Camp et al. (19) reported a curative resection rate of 79% in 105 patients with pathologically proven stage IIIA/IIIB disease treated with hyperfractionated RT and concurrent CT followed by resection and postoperative CRT. Treatment-related mortality was 9%. Median and five-year survival rates were 27 months and 32%, respectively.

Subsequent phase III trial of the GLCCG randomly assigned 524 patients with Stage IIIA/B disease to induction CT followed by hyperfractionated RT concurrent with CT then surgery or to three cycles of induction CT followed by surgery, and then further RT (control group) (20). Patients with incomplete resection or unresectable disease received additional hyperfractionated RT. Complete resection rates were 37% and 32% for the interventional and the control groups, respectively. The proportion of mediastinal downstaging (46% *versus* 29%; p=0.02) and pCR (60% *versus* 20%; p<0.0001) in these patients favored the interventional group, with no difference in the five-year progression-free survival between treatment groups (16% *versus* 14%; p=0.87). In both groups, the pneumonectomy rate was 35%. However, the treatment-related mortality rate in pneumonectomy patients was higher in the interventional group (14% *versus* 6%).

German and French groups conducted a multicenter phase II trial (CISTAXOL) and reported their 10-year long-term results in 2013 (21). Sixty-four patients with mediastinoscopically-proven IIIA(N2)/selected IIIB disease received three cycles of induction CT followed by CT concurrent with hy-

perfractionated RT. Thirty-six patients were operated on. R0 resection and pCR rates were 89% and 44%, respectively. The respective five- and 10-year survival rates were 30.2% and 26% for the whole group, 37.1% and 37.1 for stage IIIA (N2), and 26.2% and 17.9% for stage IIIB patients. This study was performed as an experimental arm of the same group's prospective randomised phase III trial (ESPATUE) (22). In this trial, surgery *versus* definitive concurrent CRT boost following induction CT and concurrent CRT was investigated. Of the 246 patients enrolled, 227 completed induction treatment. One-hundred-sixty-one operable patients were randomised to surgery or definitive concurrent CRT boost. In the surgery arm, the R0 resection rate was 81%. OS rates at five years were excellent for both treatments (44.2% for the surgery group and 40.6% for the definitive CRT group).

In another study from WGCC, the data of 239 patients treated with cisplatin-based induction CT followed by concurrent CRT using accelerated-hyperfractionation (45 Gy/1.5 Gy bid) or conventional fractionation (46 Gy/2 Gy qd) were retrospectively evaluated (23). pCR rates were in favor of the accelerated-hyperfractionation group (37% *versus* 24%; p=0.04), and it was a significant positive prognostic factor (p=0.0003). Nevertheless the influence of the fractionation schedule was not significant for survival. The five-year survival of patients with pCR was 65%, independent of the fractionation. Grade 3–4 oesophagitis was the major side-effect in the accelerated-hyperfractionation group, as expected (p=0.0002).

Radiation dose escalation through accelerated-hyperfractionation seems promising for increasing the pCR rate. This might improve prognosis through lower locoregional recurrences and higher resection rates. A recent meta-analysis comparing modified RT schedules with conventional RT reported that patients with nonmetastatic NSCLC derived a significant OS benefit from accelerated or hyperfractionated radiotherapy (24).

## NEOADJUVANT HIGH-DOSE RADIOTHERAPY AND CONCURRENT CHEMOTHERAPY

Generally, the RT dose employed in the neoadjuvant setting has been limited to 30-45 Gy because of the technical difficulty and postoperative morbidity and mortality, particularly after pneumonectomy, when higher doses were administered. With the advances in technology, it is possible to deliver higher RT doses to the tumor volume without compromising the normal tissue tolerance. The improvement in surgical techniques and perioperative care contributed as well.

The literature regarding this subject is limited. Fowler and associates (27) reported a 43% mortality rate after pneumonectomy, but not lobectomy in a phase II trial of concurrent CRT administering 60 Gy in 13 patients (25). Sonett et al. (26) reviewed the data from 40 patients who underwent pulmonary resection (29 lobectomies and 11 pneumonectomies) after high-dose RT (median 62 Gy; range 59.4–66.6) and concurrent cisplatin-based CT. No postoperative deaths were reported. Pathologic downstaging was achieved in 85% of patients, 82.5% indicated no residual lymphadenopathy, and 45% displayed a pCR. The five-year overall and disease-free survival rates were 46.2% and 56.4%, respectively, with a median follow-up of 2.8 years.

Cerfolio and colleagues (27) assessed the safety and efficacy of pulmonary resection in 104 patients after low (<60 Gy) or high dose (>60 Gy) neoadjuvant RT with concurrent CT. pCR rates favored the high dose group (28% *versus* 10%; p=0.04) (27). The major morbidity and mortality rates were similar. Pneumonectomy was a significant risk factor for morbidity. Daly and associates (28) reviewed the feasibility of pneumonectomy after high-dose RT (59.4 Gy) and two cycles of CT in 30 patients with locally advanced NSCLC. Four patients (13.3%) had died, only one after right pneumonectomy. Major morbidity occurred in five patients. The median OS was 22 months and the five-year survival rate was 33%.

After documentation of the ability to safely perform pulmonary resections after high-dose CRT, and encouraging long-term survival results, the Radiation Therapy Oncology Group (RTOG) started a prospective, multicenter, phase II trial (RTOG 02-29) to evaluate full-dose RT concurrent with CT (29). Fifty-seven patients with pathologically proven N2-3 disease were administered CT (carboplatin/paclitaxel) concurrent with 61.2 Gy RT weekly. The mediastinal nodal clearance rate was 63%. Thirty-seven patients underwent resection (34 lobectomies, 3 pneumonectomies, 76% R0, and 24% R1 resections). The two-year overall and progression-free survival rates were 54% and 33%, respectively. The two-year OS rates for patients who achieved nodal clearance, for those with residual nodal disease, and for those who did not undergo surgical resection was 75%, 52%, and 23%, respectively (p=0.0002). The two-year PFS were 56%, 26%, and 8% for each cohort (p<0.0001). The results of the RTOG 02-29 study support the role of full-dose RT on nodal clearance rates. Another randomised phase II trial (RTOG 08-39) using the same induction regimen with the addition of an epidermal growth factor receptor (panitumumab) was started by the same group.

## NEOADJUVANT CHEMORADIOTHERAPY IN STAGE IIIB DISEASE

Stage IIIB NSCLC is usually unresectable and managed with concurrent CRT. However, selected patients might benefit from surgical resection after neoadjuvant CRT. Among the

neoadjuvant CRT trials, there is a subset of patients with Stage IIIB disease. In the SWOG 8805 trial, 40% of the patients had stage IIIB disease (T4N0-1, T4N2, N3) without superior vena cava syndrome or pleural effusion (9). There was no difference in median survival for IIIA(N2) and IIIB diseases (13 months and 17 months, respectively), and two- and three-year survival rates were similar and encouraging (two-year rates of 37% and 39%, and three-year rates of 27% and 24% for IIIA and IIIB, respectively). Exploratory univariate survival analyses of the prestudy characteristics revealed that the IIIB substage T4N0-1 or Nx had a longer median survival time than all other stage subsets (28 months *versus* 13 months; p=0.07). There was no difference in the outcome of patients with T4N0-1 disease and those with T1N2 disease. When the two subgroups with the best survival were grouped together, the median survival was significantly longer when compared to all others (32 months *versus* 12 months; p=0.03). The only significant pathologic factor predicting long-term survival was negative mediastinal nodes in the specimen. The median survival time and three-year survival rate were 30 months and 44%, respectively, for the patients with negative nodes, whereas they were 10 months and 18%, respectively, for the patients with positive nodes (p=0.0005).

Other phase II studies addressed the role of neoadjuvant CRT for stage IIIB disease. Grunenwald et al. (30) surgically staged 40 patients with stage IIIB disease received induction CT and hyperfractionated RT (42 Gy/1.5 Gy bid) given in a split course. The objective clinical response rate was 73% (29 patients), and the complete resection rate was 58% (23 patients). Four patients (10%) had complete pathologic response, and 30% had complete mediastinal clearance. The five-year survival was 42% for patients having no mediastinal involvement, whereas it was 28% for patients with persistent involvement.

The Swiss Group treated 46 patients with pathologically proven and technically resectable stage IIIB disease with three cycles of neoadjuvant CT immediately followed by accelerated concomitant boost RT and surgery (31). Thirty-five patients (76%) underwent surgery (17 pneumonectomies), and R0 resection was achieved in 77%. The peri-operative mortality rate was 5.7%. The pathological mediastinal downstaging and pCR rates were 39% and 13%, respectively. The median survival was 29 months with survival rates at one, three, and five years of 67%, 47%, and 40%, respectively.

## CONCLUSION

Multimodality approaches to locally advanced NSCLC is one of the most challenging issues in the treatment of this disease. The results of phase II and III studies revealed that a neoadjuvant CRT approach in appropriately selected patients can offer improved pathologic response rates with acceptable toxicity. The delivery of neoadjuvant CRT requires multidisciplinary expertise and coordination. In the current practice guidelines of the American College of Chest Physicians, either definitive chemoradiation therapy or induction therapy followed by surgery is recommended in patients with discrete N2 involvement identified preoperatively (1).

Patient selection criteria should be defined based on individual risk profiles and carefully designed prospective clinical trials with a homogeneous patient population receiving identical CT schedules on both arms. Integrating new RT techniques should be encouraged to determine the definite role of neoadjuvant RT. The optimal timing of RT with respect to CT and surgery, as well as the optimal RT dose prescription in induction regimens, has yet to be determined. When implementing these multimodality treatments, it is important to evaluate their impact on the quality of life of the patient, which is a more important issue than a prolonged survival.

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