Journal of
Pulmonary & Respiratory Medicine

Hazem et al., J Pulm Respir Med 2018, 8:3
DOI: 10.4172/2161-105X.1000463

Research Article Open Access

Neoadjuvant Chemotherapy in Lung Cancer: Our Results after Twelve Years of Surgical Resection

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Abstract

Introduction: Lung cancer is characterized by its frequency and prognosis, which remains reserved by the fact that the diagnosis is often made at the locally evolved or metastatic stages. The aim of this study is to evaluate the contribution of neoadjuvant chemotherapy to the resectability of non-small cell lung carcinoma, while highlighting its impact on the incidence of surgical complications and the effect of this therapeutic strategy on survival.

Materials: We have carried out a retrospective analysis of patients who underwent surgical treatment of non-small cell lung cancer (NSCLC) after neoadjuvant chemotherapy (NAC), between March 2000 and October 2012 at the Thoracic Surgery Department of Abderrahmen MAMI University Hospital.

Results: During the study period, 103 patients were referred to our institution for NSCLC's curative surgery after a NAC. Ninety five (95) patients are operated and 8 were not because of tumor progression after NAC or a high risk of operative mortality. The evaluation after the NAC showed a partial response in 77 cases (75%). More than half patients (57 cases: 55.7%) had a down-staging after the NAC. Male gender, and age increase postoperative complications significantly (p=0.042). Global survival was calculated for 87 patients 85%, 56%, 50% respectively at 1 year, 2 years and 5 years. The mean survival was 25 (range: 2 to 132) months. Global survival was increased significantly with T1 status (p=0.003) and M0 status (p<0.005) before NAC and also after NAC (p=0.032). Tumor localization had a significant impact on survival (p=0.034) with best survival with tumor in middle lobe and worst survival with bilobar tumors.

Conclusion: We noticed an increased survival with age <60 years, feminine gender, well differentiated tumor, patient with no parietal involvement, NAC protocol other than Gemzar-Cisplatine, complete or partial response to NAC, pneumonectomy as the type of resection, no enlargement resection, uneventful postoperative, R0 resection, N0 status after NAC and finally pN0 status.

Keywords: Non-small cell lung carcinoma; Neoadjuvant chemotherapy; Thoracic surgery

Abbreviations: NSCLC: Non-Small Cell Lung Carcinoma; NAC: Neoadjuvant Chemotherapy; IASLC: International Association for the Study of Lung Cancer; ATS: American Thoracic Society; ERS: European Respiratory Society

Background

Lung cancer is characterized by its frequency and prognosis, which remains reserved despite the improvement of therapeutic management. Non-small cell lung carcinomas (NSCLC) are 80%-85% of lung cancers [1]. The pejorative prognosis of this cancer can be explained by the fact that the diagnosis is often made at the locally evolved or metastatic stages. Indeed, 90% of NSCLCs are discovered at these stages [2]; 30% are found in stage III, of which one third is classified as IIIA, considered as potentially resectable and two thirds are classified as IIIB, considered as a non-resectable disease except in special cases.

A Neoadjuvant treatment is therefore necessary to reduce the tumor volume (down-staging), leading to the resectability of tumors initially unresectable [3]. Neo-adjuvant chemotherapy aims not only to make possible, or to optimize, the resection of unresectable tumors from the outset or at the limit of resectability, but also to increase survival by acting early on micro-metastasis [4].

The aim of this study is to evaluate the contribution of neoadjuvant chemotherapy to the resectability of NSCLC, while highlighting its impact on the incidence of surgical complications and the effect of this therapeutic strategy on survival [5].

Materials and Method

We have carried out a retrospective analysis of patients who underwent surgical treatment of non-small cell lung cancer (NSCLC) after neoadjuvant chemotherapy (NAC), between March 2000 and October 2012 at the Thoracic Surgery Department of Abderrahmen MAMI University Hospital.

Recruitment

We included all patients, who had histopathological diagnosis of NSCLC and were operated after a NAC, combined or not to another therapy, with a curative intent. We have excluded patients operated with a palliative or a diagnostic intents.

Eligibility of NAC was based on: 1) locally advanced tumor (stage IIIA and selected stage IIIB) considered as potentially resectable; 2) and expected benefit of this chemotherapy is down-staging and R0 resection. Eligibility of surgery for NSCLC was based on: 1) accepted

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Received June 21, 2018; **Accepted** July 06, 2018; **Published** July 13, 2018

Citation: Hazem Z, Ahmed AB, Abderrahmen A, Mahdi A, Sonia O, et al. (2018) Neoadjuvant Chemotherapy in Lung Cancer: Our Results after Twelve Years of Surgical Resection. J Pulm Respir Med 8: 463. doi: 10.4172/2161-105X.1000463

morbidity and operative mortality estimation as defined by consensus; 2) sufficient pulmonary reserve after the surgery (according to classic criteria of pulmonary resection); 3) and a complete resection (R0) considered as possible. All decisions were taken by multidisciplinary meetings, including thoracic surgeons, oncologists, radiologists, and radiotherapists.

Tumors were staged based on clinical information, bronchial fibroscopy and other imaging techniques (indicated and used as defined by consensus). Before initiating the NAC, the histopathological diagnosis was confirmed by a biopsy (percutaneous or through other technique). The chemotherapy protocol comprises 2 to 4 cycles of a combined therapy based on cisplatin.

The evaluation of NAC was achieved by clinical examination, bronchial fibroscopy, thoraco-abdomino-pelvic CT scan performed 2 to 3 weeks after the end of the NAC according to RECIST criteria.

The Follow-up was performed in the Thoracic Surgery Department and the Oncology Unit in our institution. The endpoint date was set on October 31, 2013. Global survival was calculated from the date of radical surgery up to the endpoint date. We excluded from the calculation perioperative deaths and patients with exploratory thoracotomy.

Recorded data

The following parameters were recorded:1) characteristics of patients: age (at the time of surgery), gender, antecedents, general state; 2) diagnosis and staging: location, histological type (WHO 2004 classification but since 2011 adenocarcinoma tumors were classified according to IASLC, ATS, ERS), differentiation grade, TNM status and stage (7^{th} edition of IASLC applied before NAC); 3) NAC: delay between diagnosis and NAC, chemotherapy protocol (drugs, cycles number, association to a neoadjuvant radiotherapy (NAR)), evaluation of NAC (response, TNM and Down-staging), treatment of metastasis; 4) Surgery and histopathology: delay between NAC and surgery, peroperative constitutions, type of resection, postoperative complications, resection quality, pTNM status and down-staging, 5) Postoperative follow up: delay between surgery and first consultation, relapse (delay, location, treatment), survival.

Statistical analysis

Statistical analysis was performed by using SPSS® software version 20 (SPSS Ink, Chicago, IL, USA).

Numerical results were expressed on average if the variable distribution was Gaussian and on median if it were not. We used the Student's t-test for the comparison of means and the standard deviation for the comparison of percentages after verification of applicability conditions. Estimation of survival was performed according to Kaplan and Meier method. Survival data were compared using the Log-Rank test for a single variable and the Cox model for the multivariate study. The difference was considered significant if $p<0.05$.

Results

During the study period, 103 patients were referred to our institution for NSCLC's curative surgery after a NAC. Ninety five (95) patients are operated and 8 were not because of tumor progression after NAC or a high risk of operative mortality. The median age was 55.5 (range: 74 to 25) years and the sex ratio was 13.7 (males: 96 versus females: 7).

In 64 cases (62%) tumor located at right lung and in 38 cases (36.9%) in the upper right lobe. The histopathological type was an adenocarcinoma in 44 cases (42.7%) and well differentiated in 37 cases (35.9%).

Primitive tumor was classified T3 in cases 33 cases (32%), N1 in 62 cases (60%) and M0 in 81 cases (78.6%). Thus, 50 cases (48.5) were classified IIIA.

Neoadjuvant chemotherapy

The median delay between diagnosis and NAC was 5 (range: 1-32) weeks. Gemzar-Cisplatine was used in 66 cases (64%). The median of Cycles number was 3 (range: 1-8) cycles. Five patients had a second line chemotherapy and 6 patients had a NAR (concurrent in 3 cases). The evaluation after the NAC showed a partial response in 77 cases (75%). More than half patients (57 cases: 55.7%) had a down-staging after the NAC but we notice that all metastatic patients (intra or extrathoracic) kept the same M status after the NAC even if some metastasis were completely disappeared.

Surgery and histopathology

The median delay between NAC and surgery was 6 (range: 52-4) weeks. The median tumor size was 3.5 cm, with a maximum of 13 cm. In two cases the tumor was completely sterilized by chemotherapy. We noticed a loco-regional encroachment in 31 cases (30%) with 5 cases where a radical resection was impossible. Fifty three (51%) patients underwent a lobectomy and 29 patients (28%) underwent a pneumonectomy. Resection was associated with a loco-regional enlargement in 22 cases. The postoperative was uneventful in 61 cases (64.2%). The postoperative mortality and morbidity was 3.15% and 35.74% respectively. We noticed that the type of resection, patient antecedents ($p=0.673$), general state ($p=0.929$) and loco-regional enlargement ($p=0.092$) had no significant impact on postoperative morbidity, while Male gender, and age increase postoperative complications significantly ($p=0.042$).

Resection was R0 in 80 cases (84.2%). Considering the pTNM status, there was a down-staging compared to the initial status of the disease in 65 cases (63%). The down-staging was more important with T4 status, N2 status, squamous cell carcinoma (SCC) histopathological type, well differentiated tumor and Gemzar-Cisplatine NAC protocol.

Postoperative follow up and survival

The median delay between surgery and first consultation was 6 weeks. The relapse rate after radical resection was 24.3% (25 patients). The median delay between radical resection and relapse was 9.5 (range: 2 to 40) months. Ten patients had chemotherapy as a treatment of relapse.

Global survival was calculated for 87 patients 85%, 56%, 50% respectively at 1 year, 2 years and 5 years. The mean survival was 25 (range: 2 to 132) months. Global survival was increased significantly with T1 status ($p=0.003$) and M0 status ($p<0.005$) before NAC and also after NAC ($p=0.032$). Thus, the lowest survival was noticed in Stage VI. Survival is inversely proportional to the pTNMstage with a significant difference ($p=0.029$). Tumor localization had a significant impact on survival ($p=0.034$) with best survival with tumor in middle lobe and worst survival with bilobar tumors.

Age ($p=0.06$), gender ($p=0.91$), histopathological type ($p=0.26$), differentiation grade ($p=0.51$), parietal involvement ($p=0.4$), NAC protocol and response ($p=0.11$), type of resection ($p=0.95$), enlargement resection ($p=0.95$), postoperative complications ($p=0.493$), resection quality ($p=0.76$), N status after NAC ($p=0.34$) had no significant impact on survival. But we noticed an increased survival with age <60 years, feminine gender, well differentiated tumor, patient with no parietal

involvement, NAC protocol other than Gemzar-Cisplatine, complete or partial response to NAC, pneumonectomy as the type of resection, no enlargement resection, uneventful postoperative, R0 resection, N0 status after NAC and finally pN0 status.

Discussion

The NSCLC remains a major health problem, with overall 5-year survival at all stages of 17.1% [6]. Among NSCLC cases, 30% are locally advanced tumors (stage III) [7]. Multimodal treatment has become widely used in clinical practice with curative intent for Stage IIIA [8]. Patients classified in stages I and II can be effectively treated by resection of one or more lobes, in which the tumor is localized [9]. Some of these patients (stage IB and II) receive adjuvant chemotherapy based on platinum salt. Stages III constitute heterogeneous lesions making it difficult to establish a well-defined therapeutic strategy. Stage IV patients receive chemotherapy with or without targeted therapy depending on the presence of certain gene mutations [10]. Stages IV oligometastatic can receive treatment with curative intent if associated with a response to chemotherapy. Management of these patients should be discussed on a case-by-case basis in multidisciplinary meetings.

Staging and histopathology

T status is an important prognosis factor [11]. The 5-year survival of a tumor whose size is <3 cm is 64% versus 46% for tumors whose size is >3 cm [12]. Recent studies have found that tumors with a size between 0 and 2 cm have a better prognosis than those with a size between 2 and 3 cm [13]. Morgensztern demonstrated recently that tumor size is an independent prognostic factor for overall survival in Stage III [14]; patients whose tumor is classified as IIIA with a size over 7 cm are 18% more likely to die from their disease than those with a tumor size between 5.1 and 7 cm for the same stage. The chest wall involvement is often accompanied by a lymph node involvement which makes the incrimination of the influence of the invasion of the wall on the prognosis difficult. But in this case the main predictive factors affecting long-term survival are: N status, complete resection and depth of thoracic wall infiltration [15]. Overall survival does not exceed 24 months when the wall is invaded after CNA versus 60% in case of non-invaded wall. The tumors classified T4 with vascular invasion have a poor prognosis [16]. But a few cases of prolonged survival have been reported. Inoue et al. reported the case of a patient with a tumor invading the superior vena cava, who lived for 5 years and 4 months after surgical treatment [17]. Fukuse et al. showed that patients with aortic invasion had a better survival rate compared to those with left atrial invasion [18]. Nodes invasion in the presence of a T4 tumor is an important prognostic factor. Martini et al. reported that there was no long-term survivor in patients classified T4N2, so surgery is indicated only for tumors classified as T4N0 and T4N1 [16]. In a study of 12 patients with vertebral invasion treated at the Institut Montsouris in Paris, the survival rate at 3 years was 35% [19]. In our series, 2 patients had vertebral invasion. They both had a radical resection of the tumor and of the spinal extension. Régnard et al. concluded that the surgical treatment of NSLC with carina invasion yield acceptable results in terms of operative mortality and long-term survival, and that would be closely related to N status. For this type of invasion, the patients must be carefully selected. In our series, after NAC treatment and then surgery, the best survival was found in T2b patients followed by T1a and then T3. This difference is statistically significant (p=0.032). The tumor infiltrated mediastinal structures in 17.5% of cases before NAC (18 patients). The survival of tumors classified T4 before treatment does not exceed 25 months. The 5-year survival of T1, T2 and T3 tumors was 78%, 50% and 35%, respectively.

The N status of tumor is an important prognostic factor. In the operable NSCLC, subgroups of N have been identified [20]. Martini found a significant 5-year survival difference between single N1 involvement and multiple N1 involvement (45% versus 31%) [21]. Also, the prognosis of tumors with multiple N1 is similar to that of N2 tumors [22]. For tumors classified N1, the prognosis of tumors where lymph extension is restricted to stations 14, 13, 12 or 11 is better than that of tumors with station 10, and the 5-year survival of N1 tumors with involvement of station 10 is 35.1% compared with 58.6% in the absence of this station [22]. It was shown that T1-3 N2 status, with under-carinal nodes involvement was associated with a poorer prognosis with no 5-year survival compared to 29.5% in the absence of under-carinal nodes (P=0.0005). Furthermore, in a study of a group of patients with N2 lymph node involvement, different authors showed a significant 5-year survival difference between patients with multiple N2 involvement and those with single N2 involvement with 5-year survival respectively from 9 to 23% compared with 25 to 60%. There is also a difference between a Bulky-N2 and limited or discrete lymph node involvement. The survival of N2 status is also influenced by the localization of the primary tumor. Thus, Ichinose and Casali found better survival for patients with a tumor of the upper lobe (right or left) with N2 lymph node invasion [23-25]. A contralateral or supraclavicular mediastinal lymph node involvement (N3) causes the tumor to progress to stage IIIB with a 2-year survival of 11%, regardless of the tumor size. Tumors with invasion of contralateral mediastinal lymph nodes (N3) have been considered by most teams as a contraindication to curative surgery and have been associated with a zero healing rate, but some surgeons continue to suggest resection [26,27]. The proportion of N2 before NAC in our study was 60%. This proportion was 16% at histology. In our series, only one patient classified N3, treated by resection of invasive supraclavicular adenopathy followed by CNA followed by surgery remained alive until the endpoint date (overall survival at 11 months). The 2-year survival of pN2 was 30%, whereas that of pN0 was 60%.

The presence of a metastasis marks the transition from localized disease to a systemic form of poor prognosis [27].

A single metastasis can be resected with a curative intent if the primary tumor can be completely resected but the presence of invaded lymph nodesis a factor of poor prognosis and contraindicates surgery. In our series, metastases were found in 21.4% of cases (22 patients), 50% were classified M1a and 50% M1b. If there is a single operable cerebral metastasis and the primary lesion can be controlled, resection surgery should be proposed. The survival at 5 years can then reach 21.4%. Cerebral radiotherapy after metastasis resection would reduce the risk of recurrence at this level [28,29]. Unique cerebral metastases led to the discovery of the diagnosis in 5 patients included in our study (5%). These lesions were treated by surgical excision in all these cases, followed by a cerebral irradiation reported in 3 of them. The chemotherapy was then carried out followed by radical surgery before complete cerebral remission. Survival in our series was not significantly affected in metastatic cases (P=0.268). Five-year survival was 64% for M0 patients and 46% for M1 patients. Survival is better when the primary cancer is an adenocarcinoma and if there is no lymph node involvement and depended on 4 factors including PS, sex, age, and initial NSE value according to Jacot et al. [30,31]. For hepatic metastases, radical surgery has been proposed in many patients with acceptable survival whenever the primitive was deemed resectable. For adrenal metastases, surgery can sometimes be useful, with curative intent when the primary lesion is controlled and when its stage is not advanced [32]. Finally, for pulmonary metastasis, surgery remains indicated if the primitive is not very advanced especially in the absence of lymph

node involvement. Moreover, when it is unique, a synchronous cancer must be evoked. It is estimated that there are 4% of multiple cancers: 60% are metachronous, 40% are synchronous [32]. In our study, the overall survival of metastatic patients treated for curative intent did not reach 2 years. Five patients had recurrence. The recidivism could not be confirmed for the other cases.

Several recent European and American studies, showed a gradual decrease in squamous cell carcinoma in favor of adenocarcinoma [33]. In our series, we observed 42.7% of adenocarcinomas and 36.9% of squamous cell carcinomas. Numerous publications have studied the prognostic value of the histological type. However, the pejorative value given by some of these studies to SCC and by others to adenocarcinoma maintains controversary [34]. In our study, by comparing the two main histological types encountered, squamous cell carcinomas and adenocarcinomas, the survival difference was not significant (p=0.26).

Neoadjuvant chemotherapy

Consequences of preoperative chemotherapy and radiotherapy remain debated [35]. Improved survival in patients with locally advanced tumors following induction therapy has been demonstrated by several studies with an effect on control of Disease [36]. But the NAC's level of evidence is based on phase III-trials with reduced number of patients [37].

After NAC, the mediastinal down-staging was 17% and 27% respectively. The complete response was 0% and 2% [38]. In our series, and considering the pTNM stage, we noticed that there was a down-staging compared to the initial stage of the disease in 63% of the cases.

A meta-analysis of 13 controlled and randomized trials including 3224 patients demonstrated survival benefit (p=0.001) in patients treated with CNA and surgery compared with those treated with surgery alone [39]. Moreover, the best treatment remains uncertain due to the heterogeneity of the treatments received and the population in these trials. NAC had potential advantages compared to adjuvant chemotherapy such as decreasing tumor size, increasing resectability and earlier eradication of micro-metastases [5]. However, NAC may delay the time of surgery; the tumor could become unresectable and progress under chemotherapy. In our series, 13% of patients remained stable and 6% progressed under NAC. Two patients out of 95 treated with NAC were unable to benefit from surgery due to a progression of their disease.

The management of N2 tumors is widely discussed. For example, in the recently updated US recommendations, N2 diagnosed preoperatively should benefit from multi-modal treatment that can only include surgery in prospective trials [40].

A significant gain in survival can be obtained in patients with NSCLC that can be resected immediately by cisplatin-based chemotherapy, whether neoadjuvant or adjuvant [41]. In our series, the most used protocol was gemzar-cisplatin with 68%, followed by the navelbine-cisplatin protocol: 14%. Lower survival was found in patients treated with gemzar-cisplatin compared with other NAC protocols (p=0.11).

Studies have shownimproved survival of patients treated with Pemetrexed for non-squamous cell carcinomas compared to squamous cell carcinomas [42]. Hirsch et al. in their review of the literature, have demonstrated that no histopathological subtype of NSCLC has been associated with improvement or impairment of prognosis in advanced stages [43]. In our series, down-staging was more important for squamous cell carcinomas than for adenocerciomas (61% versus 43%).

Pisters reported that the proportion of patients who achieved a complete histological response (CHR) after NAC was 12% (9/27), unlike Roth who reported a 0% (0/28) rate and Rosell who reported a rate of 3% (1/30) [44]. Pisters showed that 5-year survival in stage III patients with CHR was 54% [44]. In our study, we had 14% (13 patients) of complete histological response to the tumor and lymph nodes (pT0N0): six of them were still alive, four were lost to follow-up and three died. Five-year survival in these patients was 51%.

Surgical resection

Among all therapeutic means currently available, complete surgical resection of the primary tumor associated with lymph node dissection stills the only treatment which offers a significant chance of curing bronchial cancer.

The guidelines of the "American College of Chest Physicians" of 2013 recommend minimally invasive pathways for small tumors without ganglionic involvement [45]. In our series, and given the advanced stage of the disease, the approach used was the posterolateral thoracotomy.

Okada et al. showed that tumor size is an important prognostic factor on which the choice of surgical technique depends [46]. Indeed, the 5-year survival rate for a group of patients with a stage I NSCLC with a tumor size of less than 20 mm is 96.7% after a segmentectomy, 92.4% after a lobectomy and 85.7% after a wedge resection. They concluded that the difference in survival was not significant. Wedge resection is mostly performed in patients with reduced lung capacity. In our series, the most frequent procedure was lobectomy (53 cases), followed by pneumonectomy (29 cases), bilobectomy (3 cases), Wedge resection (2 cases) and lobectomy Associated with a Wedge resection (2 cases). The resection was extended to other structures in 26 patients. Enlargement concerned the coasts in 17 cases, the rachis and the ribs in 2 cases and the left atrium in 3 cases. Patients who had no enlargement had better survival: 58% versus 47% at 2 years (p=0.95).

Wu et al. they showed that complete lymph node dissection had a prognostic impact on survival after resection of lung cancer [47]. In our series, lymph node dissection was associated with pulmonary resection for all patients treated with curative surgery [48].

According to Kim et al. (study of 233 patients operated after neo-adjuvant therapy), there was 6% early mortality and 13% delayed mortality after pneumonectomy compared to 1% and 4% respectively for lobectomy [36]. According to Martini et al. the right seat of pneumonectomy (p=0.002), peroperative hemorrhage (p=0.001) and FEV1 before surgery (p=0.001) are significant predictors of postoperative complications [48,49]. In our study, postoperative complications were observed in 34 patients (35.8%). The most frequent complications were atelectasis and pneumonic infections (20.6%), followed by prolonged aerial leakage (17.6%) and cardiac arrhythmias (14.7%). The three postoperative deaths were related respectively to: pulmonary embolism, septic shock and ARDS. Only the age had a statistically significant relationship with the occurrence of postoperative complications. A positive relationship exists between age over 60 years and the occurrence of these complications (p=0.042). Complications were more frequent after bilobectomy, followed by Wedge resection followed by lobectomy. Pneumonectomy was complicated in 34.5% of cases. Survival is better for patients with uneventful postoperative (P=0.493). We concluded that NAC did not increase the frequency of postoperative complications.

Perspectives

Based on the various prospective and retrospective studies, there

is no consensus regarding the management of tumors at the limit of resectability which remains controversial, as stated in the American College of Chest Physician Guidelines [40]. Studies are expected to clarify this topic and improve the survival of stage III patients. The gold standard for the management of these patients remains the multimodal treatment combining chemotherapy with or without neoadjuvant radiotherapy and radical surgery, followed or not by adjuvant treatment.

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