Results of surgical treatment of primary lung cancer with synchronous brain metastases

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Abstract

Introduction: The surgical treatment of non-small cell lung cancer (NSCLC) with synchronous brain metastases is more effective than other therapeutic options, but this management is still controversial. The aim of the study was to evaluate the survival of patients after pulmonary resection for NSCLC preceded by resection of brain metastases.

Material and methods: From 2007 to 2012, 645 patients underwent pulmonary resection for NSCLC at our department. In 25 of them (3.87%) thoracic surgery was preceded by resection of a single brain metastasis of NSCLC and a PET CT scan. No signs of nodal involvement or distant metastases were detected.

Results: The group consisted of 18 men (72%) and 7 women (28%). Average age was 57.62 years (46-70). In all cases, whole brain radiotherapy ($5 \times 4$ Gy) was performed. The average interval between excision of brain metastasis and lung resection was 31.4 days (27-41). Pneumonectomy was performed in 1, lobectomy/bilobectomy in 17 and wedge resection in 7 cases. Pathological stage NO was diagnosed in 17, N1 in 5 and N2 in 3 patients. Average survival was 18.68 months (4-74). Survival at 1, 2 and 5 years was 64%, 28% and 28% respectively. Average disease-free survival was 17.32 months. Histological type ($p = 0.57$) and G ($p = 0.82$) have no influence on survival. All the patients with hilar lymph node involvement died within 26 months and with mediastinal one within 12 months.

Conclusions: Surgical treatment of patients with NSCLC with synchronous brain metastases may prove beneficial in selected patients after excluding other distant metastases and lymph node involvement.

Key words: lung cancer, brain metastases.

Streszczenie

Wstęp: Leczenie operacyjne niedrobnokomórkowego raka płuca (NDRP) i towarzyszących synchronicznych przerzutów do mózgu jest skuteczniejsze niż inne opcje terapeutyczne, ale postępowanie to nadal pozostaje kontrowersyjne.

Cel pracy: Ocena przeżyć odległych u chorych operowanych radykalnie z powodu raka płuca, u których wcześniej usunięto przerzut raka płuca z mózgu.

Materyal i metody: W latach 2007–2012 operowano radykalnie 645 chorych z powodu NDRP. Sporządzono nich u 25 (3,87%) przed leczeniem torakochirurgicznym usunięto radykalnie przerzut tego raka z mózgu oraz wykonano pozytonową emisyjną tomografię połączoną z komputerową tomografią rentgenowską (positron emission tomography – computed tomography – PET-CT), nie stwierdzając zajęcia węzłów chłonnych i przeżycia doległych.

Wyniki: W badanej grupie było 18 mężczyzn (72%), średnia wiek wynosiła 57,62 roku (46–70 lat). U każdego chorego zastosowano uzupełniającą radioterapię głowy (5 × 4 Gy). Czas pomiędzy operacjami wahał się od 27 do 41 dni (średnio 31,4 dnia). Pneumonektomię wykonano u 1 chorego, lobekтомię/bilobekтомię u 17, a resekcję klinową u 7 chorych. Po operacji stwierdzono brak przerzutów do węzłów u 17, cechę N1 u 5 oraz N2 u 3 chorych. Średni czas przeżycia wynosił 18,68 (4–74) miesiąca. Przeżycie po 1, 2 i 5 latach wynosiło odpowiednio 64,0%, 28,0% i 28,0%. Średni czas wolny od nawrotu wynosił 17,52 miesiąca. Typ histologiczny ($p = 0.57$) i stopień zróżnicowania nowotworu ($p = 0.82$) nie wpłynęły na czas przeżycia.

Wnioski: Radykalne leczenie operacyjne raka płuca u chorych po uprzednim usunięciu przerzutu z mózgu jest skuteczne u wybranych chorych po wykluczeniu przerzutów odległych w PET-CT i zajęcia węzłów chłonnych metodami inwazyjnymi.

Słowa kluczowe: raka płuca, przerzuty do mózgu.
Introduction

Lung cancer is the leading cause of cancer death in both men and women in Poland [1]. Brain metastasis is diagnosed clinically in up to 30% of patients with non-small cell lung cancer (NSCLC) during the course of the disease [2, 3], and in autopsy series the incidence is up to approximately 60% [4]. Surgical resection of these metastatic lesions is considered in only 25% of patients [5]. Long-term survival after surgical treatment of metachronous brain metastases in patients with primary NSCLC has been reported in several studies and is promising [6, 7]. However, the results of surgical treatment of synchronous brain metastases along with the primary tumours is controversial [8, 9]. In this retrospective analysis we present our results of resection of synchronous brain metastases and of the primary NSCLC. In addition, we present prognostic factors affecting survival.

Material and methods

From January 2007 to December 2012, 645 patients underwent pulmonary resection for non-small cell lung cancer at our department. In 25 of them (3.87%) surgical treatment for single brain metastases from lung cancer was performed before thoracic surgery. Preoperative workup included positron emission tomography (PET) scan and magnetic resonance imaging or computed tomography (CT) scan of the brain. No signs of residual tumour of the brain, nodal involvement or distant metastases were detected. The medical records of these patients were reviewed. This record was examined for age, sex, histological type and grade, postoperative tumour and nodal stage, surgical procedure, adjuvant therapy and survival. Cerebral and pulmonary resection was considered radical if all macroscopic evidence of disease was removed. Postoperative staging was done according to the International Staging System for Non-Small Cell Lung Cancer (2008). Survival was estimated by the Kaplan-Meier method with the date of pulmonary resection used as the starting point and the date of death or last follow-up as the end point. The influence of variables on survival was analysed by the log-rank test for multivariate analyses.

Results

The group consisted of 18 men (72%) and 7 women (28%). Average age was 57.62 years (range 46-70). The average interval between excision of brain metastases and lung resection was 31.4 days (range from 27 to 41 days). Pneumonectomy was performed in 1 patient, lobectomy/bilobectomy in 17 and wedge resection in 7 patients (due to compromised cardio-pulmonary function). No patient had preoperative endobronchial ultrasound (EBUS) or mediastinoscopy. Adenocarcinoma was found in 13 cases, squamous-cell carcinoma in 8, large-cell carcinoma in 2 and others in 2 patients. Pathological stage N0 was diagnosed in 17 patients, N1 in 5 and N2 in 3 patients.

Whole brain radiotherapy (WBR) (5 × 4 Gy) was applied in every patient after the neurosurgical procedure, before lung resection. Postoperative adjuvant chemotherapy was given in 12 patients (48%). Patients were selected to receive adjuvant therapy at the discretion of the surgeon and consulting oncologist. Inclusion criteria for chemotherapy were mediastinal or hilar nodal involvement, grade G3 carcinoma (2 cases) and large-cell carcinoma (2 cases).

There were neither perioperative deaths nor serious perioperative complications after pulmonary resection. Follow-up was complete in all patients for a median of 19 months (range 4-74). Recurrence developed in 15 patients (60%). It was only local in 7 cases (47%) - 4 in the lung and 3 in the brain – and distant in 3 cases (12%): bone, adrenal, liver. In 5 cases (20%) both local and distant recurrence developed. No patient underwent late reoperation for recurrent brain metastases. Average survival time was 18.7 months (range from 4 to 74 months). Survival at 1, 2 and 5 years was 64%, 28% and 28% respectively. Average disease-free survival was 17.5 months. Currently, 10 patients are alive without evidence of recurrent disease (7 of them 60 months or more after pulmonary resection).

Cell type (p = 0.57) and G (p = 0.82) have no influence on survival. All the patients who had hilar metastases died within 26 months and those with mediastinal lymph node involvement within 12 months. No statistical significance was calculated because of the small number of cases. Multivariate analysis found that neither age (0.59), sex (0.61), tumour histological type (p = 0.57), grade (p = 0.82), type of pulmonary resection (p = 0.64), nor adjuvant chemothera- py (p = 0.71) affected long-term survival.

Discussion

Cisplatin-based chemotherapy is the gold standard of treatment of disseminated NSCLC [10]. However, solitary metastases to the brain, other lung and adrenal gland, especially metachronous, detected a long time after primary pulmonary resection, are believed resectable, with an acceptable cure rate [11]. The prognosis worsens when the time between treatment of primary tumour and diagnosis of metastasis is shorter, and is believed to be significantly worse for synchronous metastases [12], although some authors observed a better prognosis with synchronous metastases than metachronous brain metastases [9]. When the first symptoms of lung cancer are those caused by distant metastases, usually the only treatment is palliative chemotherapy. However, in recent years a growing role of local treatment (radiation or surgery) of solitary distant metastases has been stressed. An example is solitary metastases to the brain, which can be radically removed by the surgeon, treated with stereotactic radiosurgery (SRS) or gamma-knife radiosurgery (GKRS), often with adjuvant whole brain radiotherapy (WBRT) or systemic cytostatic chemotherapy, followed by radical resection of the primary pulmonary tumour, if no other local or distant metastases are present. This is quite a rare situation, in our series found only in 3.87% of resected patients, but, because lung cancer is the most common neoplasm, this accounts
for a meaningful group of patients. Most authors agree that SRS or GKRS gives similarly good local control of brain metastases as surgical resection [13-15], while WBRT is believed to provide shorter median survival [16] (15.4 months vs. 11.5 months, \( p = 0.002 \)) [14]. Some data show a slightly better prognosis after surgical resection of brain metastases than after SRS [17].

It is widely accepted that after radical treatment of solitary brain metastasis, only patients without other distant metastases and without nodal metastases can be considered candidates for radical surgical treatment. Therefore in our study PET-CT screening was always performed before thoracic surgery. Positron emission tomography–computed tomography is also considered mandatory by other authors, to exclude mediastinal nodal metastases [18]. In our series preoperative staging was based on PET screening, and patients without suspected metastases to lymph nodes were subsequently operated on. Some authors routinely performed mediastinoscopy in such patients, to exclude N2 disease [15]. However, numerous studies have proved that in patients after radical treatment of synchronous brain metastases, surgery allows better local control and longer median survival than thoracic radiation combined with chemotherapy [19, 20], although others have stressed that not the type of local thoracic radiation but response to preoperative chemotherapy was the main prognostic factor [10]. In the preoperative regime, the MVP regimen (mitomycin, vinblastine, cisplatin) was, however, poorly tolerated in a phase II trial in NSCLC patients with solitary metastases [21], while newer chemotherapeutic agents seemed to be better tolerated [22]. However, many authors did not report any chemotherapy prior to thoracic surgery.

Similarly as in our study, many authors stress that the absence of nodal metastases is the main factor influencing survival in only one paper [25].

Conclusions

Surgical treatment of patients with NSCLC with synchronous brain metastases may prove beneficial in selected patients after excluding other distant metastases and lymph node involvement. Survival after resection of the primary tumour in patients with lymph node metastases is very poor; therefore EBUS-TBNA (transbronchial needle aspiration) or mediastinoscopy should be performed routinely in this group of patients.

Disclosure

Authors report no conflict of interest.

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