

IORT and External Beam Irradiation (EBI) in Clinical Stage I–II NSCLC Patients with Severely Compromised Pulmonary Function: An 52-Patient Single-institutional Experience

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Introduction

In limited stage NSCLC surgery offers the best chance for cure [1]. However, patients who would not tolerate a radical surgical procedure such as lobectomy on the basis of severely compromised pulmonary function or cardio respiratory impairment are also poor candidates for radical external beam irradiation. These patients may benefit from alternative procedures that allow maximum sparing of adjacent lung tissue such as brachytherapy [10, 11], stereotactic radiotherapy [12–15] or IORT. There is clear evidence that loco-regional control in lung cancer is dose related [2, 3], but neighboring normal tissues such as ipsilateral or collateral lung, heart, spinal cord are limiting factors for delivering doses necessary to eradicate the primary or loco-regional metastases. The rationale of IORT, builds on the observation that only patients in whom local control has been achieved had a prolonged survival [2, 3]. IORT permits to selectively deliver high single doses to the tumor or the tumor bed with maximum sparing of adjacent normal tissue and has been applied with curative and palliative intent in a variety of tumors. Experience with IORT in lung cancer is still very limited [4–9]. The current study evaluates the outcome of combined IORT and EBI in a highly selected cohort of patients with clinical stage I–II NSCLC who were fit to undergo thoracotomy and lymph node sampling but unable to undergo lobectomy or conventional high dose EBI due to severely compromised pulmonary function.

Material and Methods

Fifty-two patients (14 females; 38 males) between 49 and 80 years of age (median: 65) with limited pulmonary reserve (median FEV1: 1.3) who were able to undergo thoracotomy and mediastinal lymph node dissection received IORT (median dose: 20 Gy; median electron energy: 12 MeV) encompassing the primary only. Four weeks after IORT conventionally fractionated EBI (median dose: 46 Gy at 2 Gy daily doses) was initiated including the primary or the primary and the mediastinum in node positive patients. Based on intraoperative findings (sizes of the primary ranged from 2–8 cm; median: 4 cm) and lymph node status 19, 21, 6, and 6 patients had stage IA, IB, IIB, and IIIA, respectively. The primary tumor was located in the upper lobe in 31, in the lower lobe in 18, and in the middle lobe in three cases. The tumors were

equally distributed between the left and right lung. According to tumor biopsy, either performed preoperatively under CT-guidance or intraoperatively, 27 patients had squamous cell carcinoma and 25 patients adenocarcinoma of which 8%, 61%, and 31% were well, moderately, and poorly differentiated.

Results

All but two patients completed the planned EBI. One patient elected to discontinue treatment after 26 Gy and another experienced a lethal bleed from his tumor infiltrating the pulmonary vessel after 28 Gy. The follow-up of the entire cohort ranges from 2 to 116 months (median: 19) and for patients alive from 2 to 116 months (median: 18), respectively.

The actuarial overall survival was 77%, 55%, 37% and the overall actuarial disease-specific survival (DSS) 74%, 60%, 48% at 12, 24, and 36 months, respectively. Females had a significantly better DSS than males ($p = 0.005$). The DSS according to stage at 12, 24 and 36 months was 87%, 71% and 61% for stage IA; 79%, 74%, and 68% for stage IB. DSS for stage IIB and IIIA patients were similar at 2-years (17%) and none of these patients survived beyond 28 months. The difference in DSS between stages IA and IB vs. IIB and IIIA was statistically significant ($p = 0.001$). The probability of DSS according to stage is illustrated in Figure 1. Neither histopathological subtype nor tumor location significantly impacted on survival. Overall actuarial metastases-free survival was 89%, 78%, and 62% at 12, 24, and 36 months, respectively. Causes of death were unrelated to tumor in 17% and tumor related in 54% patients. Two patients died from 2nd cancers and 25% are alive without evidence of tumor progression. Overall loco-regional tumor control was 73% at 12 months and 68% at 24 and 36 months, respectively (Figure 2). IORT and EBI were well tolerated without serious treatment related acute or late side effects.

Discussion

IORT alone or in combination with EBI has been used in the palliative and curative setting for the treatment of a variety of tumors [16–18] but data on IORT in NSCLC are still limited. Most investigators employing IORT in lung cancer have focused on boosting the tumor bed after resection, delivering doses up to 20 Gy with either electrons [4–8] or orthovoltage [9] with or without EBI.

Key Words: Intraoperative radiotherapy · External beam irradiation · Lung cancer

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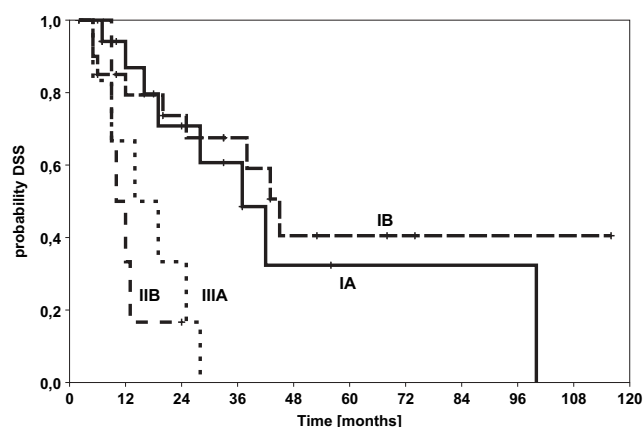


Figure 1. Probability of disease-specific survival (DSS) according to stage of disease.

The rationale for using IORT and EBI in patients with functionally non-resectable clinical stage I–II NSCL who are also poor candidates for radical EBI was to maximize the overall tumor dose by combining selective high-dose irradiation of the primary with tailored conventionally fractionated moderate dose EBI, thereby enhancing the chance of cure.

Excellent results have been reported using stereotactic irradiation in functionally inoperable patients with small peripherally located lesions [12–15], which requires irradiation under respiratory gating for maximum benefit. The majority of patients in our collective were patients with more advanced disease in whom spread to the lymph nodes is more likely expected and who would definitely not be appropriate candidates for stereotactic irradiation. The experience with brachytherapy is very limited and also includes only patients with stage I disease [10, 11].

Since 1987, 52 highly selected patients have undergone combined IORT and EBI. The results obtained in our patients compare not only favorably with results obtained with radical EBI but also with results of surgery.

Conclusion

The use of IORT to deliver high single fraction doses precisely limited to the tumor and the possibility to tailor subsequent moderate-dose EBI according to the spread of disease offers a potentially curative therapy in patients who are unable to undergo radical surgery or radical EBI due to their severe functional impairment. The results obtained are promising.

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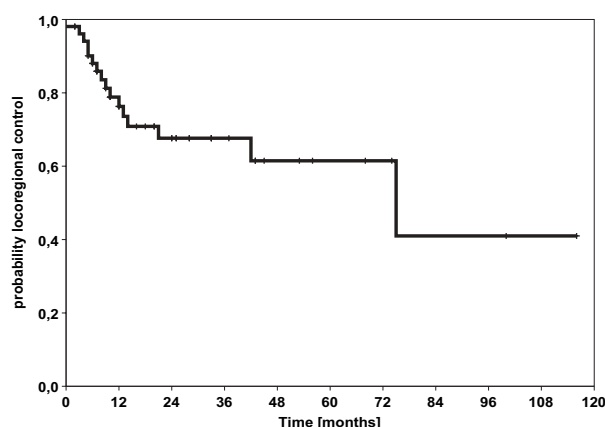


Figure 2. Probability of overall loco-regional (primary and mediastinal lymph nodes) control. =

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