Fast Neutrons for Non-Small Lung Ca/K. Saroja

Fast Neutron Beam Therapy For Non-Small Cell Lung Carcinoma

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Abstract

Retrospective analysis was performed for 63 patients with non-small cell lung carcinoma treated with fast neutrons between 1977 and 1985. The data were analyzed for local control and survival as a function of various histologies. Of 23 patients with squamous cell carcinoma, 7 had local control. Of 21 patients with adenocarcinoma, 9 had complete regression. Two of 12 patients with other carcinomas had local control; none of the 7 patients with mesotheliomas showed a response.

Three year survival rate for the group was 13%, and for patients with adenocarcinoma it was 34%. In spite of the small number of patients in each group, there is a suggestion that patients with adenocarcinoma respond better to fast neutron beam therapy.

Seven of 49 patients had treatment-related morbidity.

Key words: Fast Neutrons, Non-Small Cell Lung Carcinoma, Local Control, and Survival.
It is estimated that in 1987, lung cancer will account for 20% of all cancers in males and 11% in females. It is now the leading cause of cancer related deaths in both men and women, comprising 36% and 20% respectively of all cancers.\textsuperscript{1} Surgery remains the best therapy for patients with early stage operable non-small cell lung carcinomas. Unfortunately only one-third of patients are eligible for surgical resection at the time of the initial diagnosis. Definitive radiation therapy is indicated for the patients who are unresectable by virtue of local tumor extension, and for those with resectable tumors who are inoperable because of concurrent diseases.

The Radiation Therapy Oncology Group (RTOG) has demonstrated that high dose conventional radiation therapy can effectively achieve local control within the thorax and this can influence long term survival.\textsuperscript{2,3} The Radiation Therapy Oncology Group also conducted a randomized three arm study comparing fast neutron radiotherapy, mixed beam (neutron/photon) radiotherapy, and conventional radiotherapy, for patients with non-small cell carcinoma of lung.\textsuperscript{4}

Fast neutrons have been used to treat patients with locally advanced non-small cell carcinoma of the lung at the Neutron Therapy Facility at Fermi National Accelerator Laboratory since January 1977. Local control, survival, and complication rates
among 42 patients initially treated have been reported.\textsuperscript{5} This paper is an update including both previously treated and more recently treated patients.

**Materials and Methods**

**Technique**

The neutron beam available at Fermilab is a high-energy fixed horizontal beam delivered in an isocentric mode to patients immobilized in a sitting or standing position. A chair with capabilities of lateral, front-to-back and rotational movements is used.

A total of 63 patients with non-small cell lung carcinoma were treated with fast neutrons at the Neutron Therapy Facility at Fermilab between January 1977 and December 1985. There were 42 males and 21 females, male to female ratio 1.9. Ages ranged between 29 and 83 years. Median and mean ages were 59 and 62 years respectively. Twenty-three patients had squamous cell and twenty-one had adenocarcinoma. Twelve patients had other varied histologies. Of these 56 patients, 48 were classified as Stage III, using the T.N.M. staging classification (Table1) proposed by
American Joint Committee on Cancer. Only 4 patients had Stage I and two had Stage II disease. Two patients had local recurrent disease after the primary surgical approach and seven patients with mesotheliomas were not staged.

A total of 18 patients received chemotherapy following neutron radiotherapy. The agents used included Cyclophosphamide, 5-Fluorouracil, Adriamycin, Methotrexate, Vincristine, and Procarbazine in various combinations. Two patients who received DTIC, Adriamycin, and surgery prior to neutron beam therapy had recurrence after their primary surgical resection, and were referred for neutron beam therapy for recurrent disease. Neutrons as post-operative adjuvant therapy for residual microscopic disease was used in only one patient. Patients with Stages I and II disease were accepted for therapy either because they refused surgery or other medical problems prevented them from having a major surgical procedure.

Treatment planning involved simulation and computer generated isodose distributions. The treatment volume encompassed primary gross tumor with a 2 cm margin. The regional nodes were treated as indicated for microscopic disease. Total doses varied between 12 Gy and 21 Gy, in 6-12 fractions over 2.5-4 weeks. Most commonly the primary tumor received 21 Gy and approximately 14 Gy were given to regions with suspected microscopic disease. Careful
treatment planning was done to keep the spinal cord dose within its tolerance of 12.5 Gy. A typical isodose distribution is shown in Figure 1.

Most of our patients were followed at our facility on a regular basis at 2 to 3 month intervals for the first 2 years and every six months thereafter. Out-of-state patients had follow-up examinations by their local oncologists and evaluations were sent to us. A follow-up examination included determination of local tumor status and normal tissue late radiation changes. Appropriate investigative procedures including CT scans, X-rays of the chest, and bone scans were ordered as indicated.

All patients were followed indefinitely or until death with a median follow-up period of 8 months. Survival ranged from 1 to 49 months.

Autopsies were requested and 12 were performed. The results are incorporated in this paper.

Joint EORTC/RTOG scoring system (Table 2) is used to score the late morbidity in these patients.
Results

Local Control

Local tumor control and survival with respect to various histologies were the end point of this analysis (Table 3).

Nine of 21 patients with adenocarcinoma had initial complete response to neutron beam therapy (43%); only one of these 9 patients developed local recurrence 36 months after neutron beam therapy. In 23 patients with squamous cell carcinoma, 7 had their tumor completely regress. Excluding mesothelioma patients, none of whom showed response, the overall local complete response rate was 32% (18/56). Partial responders were grouped with patients who had persistent disease, and hence were not analyzed separately.

Survival

There are 7 patients who are alive and are free of both local and distant disease. Their respective histologies and clinical status to date are shown in Table 4. The influence of histology on the duration of survival cannot be definitely determined because the numbers in each group are small. However, there is some indication that patients with adenocarcinoma whose disease is
controlled locally survive longer than patients with squamous cell carcinoma.

Figures 2 and 3 depict survival data of 56 patients with non-small lung carcinoma by various histologies.

Observed survival is counted in months from the first day of neutron irradiation.

Survival by local control is calculated by counting a patient as "controlled" when he or she had no evidence of cancer in the area treated with neutrons or "failed" when cancer was present in the treated area, regardless of whether the patient had actually died or not.

The median observed survival time for 56 carcinoma patients is 8.7 months and the survival rate at 36 months is 13%. When the data are analyzed by local control, median observed period of survival was 11.2 months, along with a survival rate at 36 months of 27%.

When analysis was done by various histologies an interesting observation evolved. Median observed survival time for patients with adenocarcinoma was 10.3 months and survival rate at 3 years was 19%. However when the disease was locally controlled, there
was noticeable improvement in 3 year survival to 34% though there
was not much change in median observed survival period, 11.7
months.

In contrast, median observed survival time for patients with
squamous cell carcinoma was only 7.7 months and 3 year survival
rate was 9%. When the local disease was controlled, median
observed survival and 3 year survival were 10 months and 12% 
respectively.

The 12 patients with other histologies had a median observed
survival period of 6 months, with a 3 year survival period of 8%.

For patients with mesotheliomas, the median observed survival
period was only 3.3 months.

Treatment Related Morbidity

The EORTC/RTOG system was used to score the degree of late
morbidity in these patients. Only patients who survived 3 months
or longer were considered in evaluating the late normal tissue
effects. Of 49 such evaluable patients, 7 were classified as
Grade 3 or greater morbidity (14.3%).
Table 5 summarizes the experience with patients having a moderate to severe degree of morbidity. There was one treatment related death. None of our patients developed radiation myelitis.

**Autopsy Series**

There were 12 autopsies performed. Findings included embolic phenomenon in smaller vessels, fibrosis, and bronchopneumonia. These findings were not specific to neutron radiation therapy. However severe mediastinal fibrosis in one patient resulted in his death. Out of 12 autopsies, 2 had no tumor and 10 had residual or persistent disease.

**Patients with Palpable Supraclavicular Nodal Disease**

There were 13 patients who had palpable supraclavicular disease at the time of initial presentation. Six of these had local complete response; one is alive and free of disease at 49 months.
Discussion

Conventional photon radiotherapy has been used for the treatment of patients with non-small cell lung carcinoma for a number of years. Radiotherapy indications, techniques, and dose prescription have been well established and results of treatment along with survival data have been published.\textsuperscript{2,3} However, definitive data regarding neutron beam therapy for the treatment of locally advanced non-small cell lung carcinoma are not yet available.

The Radiation Therapy Oncology Group (RTOG), conducted a randomized three arm study comparing fast neutron radiotherapy, mixed beam (neutron/photon), and conventional radiotherapy for patients with non-small cell carcinoma of the lung. Results of this study suggested an improved 3 year survival on both the neutron and mixed beam arms, for the subset of patients who had complete or partial tumor response at 6 months. Survival rates were: neutrons 25\%, mixed beam 37\%, and photons 12\%. No significant differences were noted in the local response rates (neutrons 55\%, mixed beam 53\%, and photons 59\%). Median survival among the three groups of patients was neutrons 6.9 months, mixed beam 8.1 months, and photon arm 7.5 months.\textsuperscript{4}
Our results, in terms of overall local control of 32%, are lower than the above series and the series reported from Japan where Tsunemoto et. al. reported a local control rate of 45.4%. Our observed median survival time of 11.2 months and three year survival of 27% are similar and comparable to the study cited above for the neutron beam arm. The improvement in survival seen in our patients when the local disease is controlled agrees with the findings of others and further, emphasizes the need for aggressive local treatment in lung carcinoma patients.

Patients with adenocarcinoma apparently had a higher local control rate and also a greater 3 year survival, with local disease controlled, than similar patients with squamous cell histology (43% versus 30% and 34% versus 12%). This observation needs further confirmation.

For patients who were treated with conventional radiation therapy, Petrovich, et. al. reported median survival of 8 months for patients with adenocarcinoma and 14 months for patients with squamous cell carcinoma. Though their data were not specifically analyzed for local control by different histologies, patients with small cell carcinoma had a greater rate of local tumor regression than the patients with other cell types which included patients with squamous cell, or large cell carcinomas (52% versus 36%).
Tsunemoto et al. have reported their experience with 37 patients with inoperable lung carcinoma treated with mixed schedule or fast neutron boost. The survival rate at the 4 year follow-up was 11/31 (27.2%). The local control rate evaluated at 6 months was 17/37 (45.4%). Of 12 patients with symptoms typical of pancoast tumor of the lung, 9 were locally controlled and their symptoms improved markedly. Similarly one patient in our series with typical symptoms of pancoast tumor not only had relief of symptoms but also had complete response.

This finding of better response of adenocarcinoma patients to neutron therapy supports previous observations of ours and of others that slow growing well-differentiated tumors respond well to high LET neutron radiation therapy.11,12,13

Morbidity in this series is 14%, which is considerably lower than reported by RTOG (30%)4 and none developed radiation myelitis.

Conclusion

Aggressive local control measures are worth undertaking for patients with non-small cell lung carcinoma since this improves survival.
Neutrons may be indicated for patients with adenocarcinoma of the lung. Our findings need further confirmation.
References


TABLE 1

TNM Classification

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Tumor either proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically or cannot be assessed.</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ.</td>
</tr>
<tr>
<td>T1</td>
<td>A tumor that is 3.0 cm or less in greatest diameter, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.</td>
</tr>
<tr>
<td>T2</td>
<td>A tumor more than 3.0 cm in greatest diameter or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung, and there must be no pleural effusion.</td>
</tr>
<tr>
<td>T3</td>
<td>A tumor of any size with direct extension into an adjacent structure such as the parietal pleura or chest wall, the diaphragm, or the mediastinum and its contents; a tumor bronchoscopically demonstrable to involve a main bronchus less than 2.0 cm distal to the carina; any tumor associated with atelectasis or obstructive pneumonitis of an entire lung or pleural effusion.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal Involvement (N)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Minimum requirements to assess the regional nodes cannot be met.</td>
</tr>
<tr>
<td>NO</td>
<td>No evidence of involvement of regional lymph nodes.</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension.</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to lymph nodes in the mediastinum.</td>
</tr>
</tbody>
</table>
Distant Metastasis (M)

**MX**  Minimum requirements to assess the presence of distant metastasis cannot be met.

**M0**  No evidence of distant metastasis.

**M1**  Distant metastasis present.

Specify ______________

Specify sites according to the following notations:

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th>PUL</th>
<th>Bone marrow</th>
<th>MAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osseous</td>
<td>OSS</td>
<td>Pleura</td>
<td>PLE</td>
</tr>
<tr>
<td>Hepatic</td>
<td>HEP</td>
<td>Skin</td>
<td>SKI</td>
</tr>
<tr>
<td>Brain</td>
<td>BRA</td>
<td>Eye</td>
<td>EYE</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>LYM</td>
<td>Other</td>
<td>OTH</td>
</tr>
</tbody>
</table>

Stage Grouping

Occult Stage:  TX, NO, M0

Stage I:  Tis, NO, M0
  T1, NO, M0
  T1, N1, M0
  T2, NO, M0

Stage II:  T2, N1, M0

Stage III:  T3 with any N or M
  N2 with any T or M
  M1 with any T or N
TABLE 2
RTOG/EORTC Late Radiation Morbidity Scoring Scheme

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough).</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough).</td>
<td>Severe symptomatic fibrosis or pneumonitis. Dense radiographic changes.</td>
<td>Severe respiratory insufficiency/continuous 02/assisted ventilation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slight radiographic appearances.</td>
<td>Low grade fever/patchy radiographic appearances.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>None</td>
<td>Asymptomatic or mild symptoms/transient T wave inversion and ST changes/sinus tachycardia 110 (at rest).</td>
<td>Moderate angina on effort/mild pericarditis/normal heart size/persistent abnormality T wave and ST changes/Low ORS.</td>
<td>Severe/angina pericardial effusion/constrictive pericarditis/moderate heart failure/cardiac enlargement/EKG abnomalities.</td>
<td>Tamponade/severe heart failure. Severe constrictive pericarditis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 3

**Neutrons versus Histology**

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Patients</th>
<th>Local Control</th>
<th>Pers. Disease</th>
<th>Reg. Disease</th>
<th>Distant Mets Only</th>
<th>Rec. + DM</th>
<th>Local Rec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell cancer</td>
<td>23</td>
<td>7</td>
<td>16 *Δo</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(30%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>21</td>
<td>9</td>
<td>12 *θ†</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(43%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misc.</td>
<td>12</td>
<td>2</td>
<td>10 *χ§</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mesotheliomas</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>18</td>
<td>45</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(29%)</td>
<td></td>
<td></td>
<td></td>
<td>(71.4%)</td>
</tr>
</tbody>
</table>

NOS not otherwise specified.

*DM status unknown in one patient.

- Six patients had distant mets also.
- Five patients had DM and regional disease.
- One patient in each group had regional disease.
- Four patients in the group also developed DM and regional disease.
- Four patients developed DM.
- Five patients also had DM and regional disease.
- Three patients had DM.
### TABLE 4

**Neutron Therapy for Lung Cancer Survivors**

<table>
<thead>
<tr>
<th>I.D. No.</th>
<th>Histology</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>82-133</td>
<td>Adeno. ca.</td>
<td>Female, Stage III, received FAM chemotherapy after neutrons for one year, alive, NED 49 months post-therapy. Recently diagnosed to have pancytopaenia, of undetermined etiology.</td>
</tr>
<tr>
<td>83-080</td>
<td>Sq. cell ca.</td>
<td>Male, Stage III, alive, NED 36 months post-therapy.</td>
</tr>
<tr>
<td>83-090</td>
<td>Poorly diff. Large cell</td>
<td>Female, Stage III, alive &amp; well, 32 months post-therapy, (see Table 5, &quot;Morbidity&quot; for details).</td>
</tr>
<tr>
<td>84-057</td>
<td>Adeno. ca.</td>
<td>Male, Stage II, alive, NED 24 months post-therapy.</td>
</tr>
<tr>
<td>84-067</td>
<td>Adeno. ca.</td>
<td>Female, Stage IV, alive, well, NED 21 months post-therapy.</td>
</tr>
<tr>
<td>85-029</td>
<td>Sq. cell ca.</td>
<td>Male, Stage III, alive, NED 18 months post-therapy.</td>
</tr>
<tr>
<td>85-099</td>
<td>Sq. cell ca.</td>
<td>Male, Pancoast tumor of left apex with associated neurological syndrome. Received 20.4 neutron Gy. in 12 fractions over 26 days. Improvement in clinical symptoms noted. Tumor regressed in size. Underwent resection of residual mass, partial resection of T1-T2 vertebra, &amp; 2nd &amp; 3rd left ribs. On microscopic exam, residual mass contained only fibromyxomatous tissue and no tumor cells. No surgical or post-op complications. Wound healed well. Patient alive and well 12 months post-neutron therapy.</td>
</tr>
</tbody>
</table>
### TABLE 5

#### Neutron Therapy for Lung Cancer

**Morbidity**

(RTOG/EORTC Scale 3 or Greater)

<table>
<thead>
<tr>
<th>I.D. No.</th>
<th>Grade</th>
<th>Neutron Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>77-107</td>
<td>3</td>
<td>14/7/22</td>
<td>Squamous cell, Stage III. Patient died 6 months following neutron beam therapy. On autopsy no cancer cells were identified but there was extensive pneumonitis involving both lungs.</td>
</tr>
<tr>
<td>82-058</td>
<td>3</td>
<td>18/9/29</td>
<td>Squamous cell, Stage I ($T_2N_0M_0$). Severe COPD was diagnosed prior to neutron therapy. Expired 18 months post-therapy. Chest X-ray revealed dense fibrosis.</td>
</tr>
<tr>
<td>83-090</td>
<td>3</td>
<td>19.5/12/39</td>
<td>Poorly differentiated large cell carcinoma, Stage III. 15 months following neutron therapy developed shortness of breath. Pericardiocentesis followed eventually by pleura pericardial window. Cytology had revealed malignant cells? Received Cis-Platinum, Velban, Cytoxan, Adriamycin, Methotrexate, Procarbazine, 5-FU, following neutrons for 24 months. Recent chest X-ray negative for tumor but had dense fibrosis. Patient is alive and well 32 months post-therapy. Has generalized tingling sensations in all extremities which is attributed to chemotherapy.</td>
</tr>
<tr>
<td>85-029</td>
<td>3</td>
<td>22/12/26</td>
<td>Squamous cell carcinoma, Stage III. Has intermittent cough and pleural effusion. Cytology is negative for malignant cells. Dense fibrosis on chest X-ray. Patient is alive 18 months post-therapy.</td>
</tr>
<tr>
<td>77-112</td>
<td>4</td>
<td>14/7/22</td>
<td>Adenocarcinoma, Stage III. Graded such because of diffuse infiltration and scarring. The possibility of an abscess was suspected in the treated volume. Expired 11.75 months post-therapy.</td>
</tr>
<tr>
<td>80-226</td>
<td>4</td>
<td>13.2/6/35</td>
<td>Adenocarcinoma, Stage III. Developed pneumonitis, trachitis, and esophagitis a few weeks after completion of treatments. Required steroids. Expired 9 months post-therapy.</td>
</tr>
</tbody>
</table>
Patient had undergone right lower lobectomy for Stage I ($T_1N_0M_0$), squamous cell carcinoma. Received neutrons for microscopic disease. Expired 6.75 months following completion of treatments. On autopsy severe pulmonary and mediastinal fibrosis was found. This fibrosis resulted in respiratory insufficiency causing death.
FIGURE CAPTIONS

Figure 1 - Typical Isodose.
Figure 2 - Observed Survival.
Figure 3 - Survival by Local Control.
Figure 2
Observed Survival
Figure 3
Survival by Local Control