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RECENT ADVANCES IN OPTIMIZING RADIATION THERAPY IN LUNG CANCER

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PURPOSE

Eradication of local-regional disease is an essential step for an improvement in survival for patients with stage III non-small cell lung cancer (NSCL). The current radiation dose-fractionation schedule of 60 Gy administered in 30 fractions (F) over a period of 6 weeks (wks) is ineffective in providing local tumor control to the majority of patients with stage III NSCLC. Even when radiation therapy (RT) is combined with chemotherapy (CT), local failure rate still remains high at 70% although distant failure rate is reduced. To address the clinical impact of the low rate of local tumor control using the current dose schedule of 60 G/30 F/6 wks, radiation dose to the gross tumor has been escalated to 80 Gy in a number of phase I studies using 3-dimensional (3-D) conformal RT.

The aim of this presentation is to update the recent advances in radiation dose intensification/ escalation studies and translational research in predictive factors of radiation response which may be able to guide high dose RT in chemo-radiation (CT+RT) for better therapy outcome.

METHODS

The current literatures (1985-2001) on the escalation of radiation dose/intensity studies were reviewed for the progress in optimizing radiation therapy in lung cancer. Data on the current translational research in biological, molecular, and genetic markers for therapy response to RT or CT+RT were also reviewed for identification of useful biomarkers in predicting therapy response. Reports on combined therapy for stage III NSCLC were also reviewed for the toxicities, therapy response and survival outcome.

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RESULTS

The predictive factors for both the natural history and the therapy outcome of NSCLC are grouped as follows.

1.Tumor related factors (anatomic factors): The extent of tumor (tumor stage) is one of most important prognostic factors affecting the therapy outcome. Tumor size (T stage), anatomical structures involved (T4 vs. T3 lesion), and the presence or absence of regional lymph node metastasis have a significant impact on both prognosis and response to appropriate therapy.

2. Host-related factors:
Clinical factors that are important in therapy response include performance status, weight loss more than 10% of body weight in the previous 6 months, and associated co-morbidities, i.e., pulmonary and cardiac diseases.

3. Biologic markers:
Molecular/ radiobiological/ metabolic markers resulting from genetic lesions in lung cancer are grouped as follows: (a) Oncogene amplification and overexpression (aberrant gene expression) - ras , myc , HER-2/neu, p53, tubuline gene mutation, survivin gene; (b) Radiobiological factors - The surviving fraction of tumor cells at 2.0 Gy of radiation (SF2) as a measure of intrinsic tumor cell radiosensitivity, potential doubling time (TPot) as a measure of the rate of tumor cell proliferation and gamma factor representing the slope of the survival curve at 50% survival rate are being investigated as potential predictor for therapy response; (c) Enhanced metabolic rate: Increased glucose utilization measured with PET-FDG may be a useful marker for therapy response to RT and CT, and also for the definition of biological tumor volume as opposed to anatomic tumor volume defined by computed tomographic scan.

4. Radiotherapeutic factors
The successful outcome of radiation therapy depends on a clear definition of target volume, the optimal radiation dose and fractionation schedules, and proper radiation portal arrangements to secure the optimal dose distribution within the target volume and the best possible therapeutic ratio.

a. Three-Dimensional (3-D) Conformal Radiation Therapy
Significant progress has been made in 3-D conformal RT in lung cancer. With the detailed anatomical information of the primary tumor, nodal status and

normal organs provided by CT scan of the chest obtained at CT simulation, radiation dosimetry is improved for better normal tissue sparing and enhanced therapeutic ratio. Every effort should be made to achieve the best possible treatment plan, which would provide an adequate coverage of the target volume with a 95% or higher level of the prescribed dose while the differential in radiation dose between the tumor volume and the surrounding normal tissue is kept to the maximum.

Dose-volume histogram (DVH) for normal organs and tumor in 3-D conformal treatment plan is an invaluable tool to determine the optimum treatment plan. Treatment plan should be optimized to achieve the desired level of tumor control probability (TCP) while normal tissue complication probability (NTCP) is kept minimal. Intensity modulated photon and proton beam therapy has a great potential in improving these goals.

b. Target Volume

The use of a tight margin beyond the gross tumor may increase the risk of a geographic miss and inevitable local recurrence. Excessive margins, on the other hand, can increase the incidence and severity of radiation toxicities, and allow only suboptimal radiation doses to be used. A compromise between these two extremes seems most reasonable until new imaging techologies, better than the current CT scan, becomes available for improved definition of the gross tumor volume (GTV) and subclinical disease.

Treatment planning in accordance with the recommendations of the ICRU 50 report requires the definition of a clinical target volume (CTV), which must encompass the gross tumor and subclinical disease and possibly involved lymph nodes. The CTV must be expanded to a planning target volume (PTV) by some geometrical margin. This margin must guarantee adequate coverage of the CTV during treatment and should therefore be based on the accuracy of the target definition, knowledge of target movement with respect to the treatment fields, and machine accuracy (e.g. reproducibility of the block positions). An accurate definition of GTV is often difficult even with CT scan and MRI and this may be improved by newer imaging techniques such as PET scanning. An analysis of the systematic and random errors in internal organ movements and external setup errors can help in determining CTV-PTV margins. However, as such data are currently limited for patients with lung cancer, a reasonable compromise would be to apply the following guidelines.

For a locally advanced unresectable lung cancer (T1-3N2-3M0, T4N0-1M0), GTV includes the primary tumor (GTVp) and involved regional lymph nodes (GTVn), as well as tumor extension determined on the basis of bronchoscopy, mediastinoscopy and thoracotomy. The CTV, a margin allowed for potential microscopic tumor around the primary tumor (CTVp) varies from 0.7 to 1.0 cm of clinically uninvolved lung around the primary lesion depending upon the patient's pulmonary reserve. An additional 0.8 to 1.0 cm margin is added to the CTVp as a planning target volume (PTV) to take into account the setup error and patient motion. Thus, we have used a 1.5 to 2.0 cm radial margin (a combination of CTVp and PTV) and a 2.0 to 2.5 cm cranial and caudal margins for GTVp . Dose prescription is specified for the adequate coverage of the target volume, i.e., the minimum dose to the PTV is a 95% level of the prescribed dose. The CTV for involved hilar and mediastinal lymph nodes includes a 0.7 to 1.0 cm radial and a 1.5 to 2.0 cm cranial-caudal margin for the coverage of one sentinel nodal station beyond the involved lymph nodes. An additional 1.0 cm margin is added to the CTVn as a planning target volume (PTV) to take into account the setup error and patient motion. The CTV for involved mediastinal nodes at mediastinal nodal stations 7 and 4R includes 4L, 5, 6, 2R and 2L nodal stations. The inferior border of the mediastinal nodal PTV is at the level of a margin of 2.0 to 2.5 cm beyond the involved nodes at station 7 caudally. The surrounding normal structures such as esophagus, aorta, vertebrae and heart are excluded from CTV as much as possible. It should be emphasized that this is a guideline for clinical research in dose escalation using 3-D conformal radiotherapy. Clinical data on recurrence at the CTVp and CTVn needs to be collected for further refinement of such a guideline.

Interpretation of data on regional failure in the adjacent elective nodal stations should be made with great caution even in 3-D conformal radiation therapy. Even when GTVp and GTVn were the only intended target for 3-D conformal RT, incidental dose to the adjacent elective nodal stations in the mediastinum was found to be substantial. Martel et al. reported from such a study that the percent volume of the elective nodal groups receiving 50 Gy was as follows: ipsilateral hilum: 100%, contralateral hilum: 40%, subcarinal: 96%, low paratracheal 68%, aorto-pulmonary window: 49% and high paratracheal region: 2%. The estimated tumor control probability were: ipsilateral hilum: 99%, contralateral hilum: 57%, subcarinal: 97%, low paratracheal 59%, aorto-pulmonary window: 57% and high paratracheal region: 0%. Therefore, the low recurrence rate reported at the elective nodal stations

was not without substantial dose of incidental radiation dose. Future reports on recurrence rate at the adjacent elective nodal stations should be accompanied with incidental radiation dose administered unintentionally.

c. Optimal dose and fractionation schedules

There are several different fractionation schedules which have similar biologic effects on both normal and malignant tissues. The linear-quadratic formula supplemented with information on repair half times and on doses recovered per day has been advocated for comparison of the effect of different fractionation schedules on both normal and tumor tissues. An optimal fractionation schedule for lung cancer is a radiation therapy program that gives the best possible control of local-regional tumor with the fewest complications. Clinical studies on the relation between radiation dose and local tumor control have demonstrated that there is a reasonable correlation between radiation dose and tumor control in lung cancer. Other important factors for control of local-regional tumor, in addition to radiation dose, are the tumor size and stage, and the patient's general condition.

The current standard dose schedule for definitive radiation therapy consists of a total dose of 60 to 66 Gy, given with daily dose fractions of 1.8 to 2.0 Gy, five days a week over a period of 6 to 7 weeks. However, this level of radiation dose schedule is less than the optimum in providing local tumor control to the majority of patients. Radiation therapy administered in a split course, in which a rest period of 2 to 3 weeks is given at the halfway point of the entire course of treatment (5-6 weeks), has been proved to be inferior to the standard fractionation schedule without a break. New approaches aimed for an improvement in local-regional tumor control, over that attained using current radiation dose schedules combined with cisplatin based chemotherapy, are being studied as uncontrolled local-regional tumor continues to be the major source of distant metastases and eventual failure.

Accelerated or hyperfractionated radiation therapy may exploit the radiobiological advantages of both a reduced fraction size for late-reacting tissues (lung, spinal cord, connective tissue) and a shortened overall treatment time against rapidly proliferating tumors such as lung cancer. Repair time of sublethal radiation damage in aerobic mammalian cells varies from two to four hours for in vitro as compared with a period up to 6 hours for in vivo studies respectively. When a rapidly proliferating tumor cell population such as lung cancer is growing in normal tissue whose cells are nonproliferative or slowly proliferating, greater radiotherapeutic efficacy is expected with the use of two or three treatment sessions per day with normal or preferably decreased dose per fraction to maximally tolerated total doses and with intervals of at least 6 hours between fractions. Examples of accelerated and hyperfractionated radiation therapy are CHART and other twice daily or three times daily (TID) treatment schedules. A modified TID schedule of CHART with weekend off (CHARTWELL) and escalated total doses up to 60 Gy with or without chemotherapy is presently tested by several groups. In a phase II study by the Eastern Cooperative Oncology Group (ECOG) with radiation dose of 5760 cGy in 36 F, TID over a period of 15 days with weekend off, grade 3 acute esophagitis was observed in 21% (6/28) of patients. The overall objective response rate, median survival and 1-year survival rate were 54%, 13 months and 57%. However, the optimum radiation dose schedule for stage III NSCLC remains to be determined. Accelerated dose schedule such as CHART or CHARTWELL with or without dose escalation needs to be tested in a setting of concurrent chemo-radiotherapy.

There are on-going radiation dose escalation studies using 3-D conformal therapy and a daily treatment schedule. The maximum tolerated dose of radiation depends on the size of GTV and DVH of normal organs, i.e., lung DVH. For small T1 lesion, MTD was not met even at 80 Gy.

5. Timing of Chemotherapy and Radiotherapy

It has been demonstrated that chemo-radiotherapy is better than standard radiation therapy alone for survival in stage III NSCLC. Arriagada and Le Chevalier showed in one of their studies that a sequential combination of chemotherapy and radiation therapy resulted in a decrease in the metastatic failure rate from 70% of radiotherapy alone to 49% by the combined therapy, and that this decrease in distant failure rate led to an improvement in survival. However, there was no difference in local control rate between the two groups. Schaake-Koning et al. showed that radiation therapy combined with daily cisplatin was more effective than radiation therapy alone in achieving local tumor control and this improved local tumor control was translated into survival gain. Indeed, Furuse et al. conducted a phase III study in which a concurrent versus sequential radiation therapy in combination with mitomycin, vindesine, and cisplatin was compared in unresectable stage III NSCLC. The concurrent combination of chemo-radiotherapy was more effective than sequential combination in overall response and survival time. The median survival time, 3- and 5-year survival rates were

16.5 months, 22% and 16% by the concurrent combination as compared with 13.3%, 15% and 9% by the sequential combination. The therapeutic advantage of the concurrent combination was realized even with the inferior radiation dose schedule employed in this study: 56 Gy in 28 fractions over a period of 7.6 weeks versus 56 Gy in 28 fractions over a period of 5.6 weeks for the concurrent versus sequential combination respectively. More studies are needed to define the optimum timing of chemotherapy and radiotherapy in combined chemo-radiotherapy.

CONCLUSION

Current data indicate that there is a dose-response relationship between radiation dose and local tumor control, and also between local tumor control and survival in stage III NSCLC. Therefore, the radiotherapeutic factors, i.e., total radiation dose, fractionation schedule and dose intensity, the use of 3-D conformal radiation to secure the optimum therapeutic ratio are important in improving local tumor control and survival. Future research should be directed towards radiation dose escalation using 3-D conformal therapy to determine the maximum tolerated dose (MTD) of radiation in a setting of chemo-radiotherapy, and the use of this MTD for better outcome. Radiobiological, molecular, and metabolic markers may have potential for monitoring tumor response and optimizing radiation therapy accordingly.

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