FUNCTIONAL EVALUATION OF POSTRADIATION LUNG INJURY

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INTRODUCTION

Thoracic irradiation is often used in the management of patients with cancer of the breast, lung or eosophagus, Hodgkin's and non-Hodgkin's lymphomas, and mediastinal neoplasms. The lung is a dose limiting organ and extent of radiation-induced pulmonary injury depends on the irradiated volume, total dose, fractionation and radiation energy applied (Penney et al, 1994; Roach III et al, 1995). There are three phases of lung response to radiation: the early phase (latent period of pneumonitis; first month), the intermediate phase (acute pneumonitis; 1-6 months) and the late phase (fibrosis; after 6 months) (Rubin and Casseratt, 1968). Acute radiation pneumonitis, a clinical syndrome including dyspnoe, cough, fever and chest pain, occurs in 5 to 15% of patients irradiated to the chest (Gross, 1977).

The unaffected pulmonary function is of critical value and even its small reduction may have clinical significance, particularly in patients with long-term survival. Postradiation lung injury may also have a considerable impact on patient's quality of life. Avoiding of this sequelae of radiation and its effective management is therefore of particular importance.

Standard methods of detection and grading of postradiation pulmonary toxicity have until recently been based on clinical sign and symptom scoring and on radiological evaluation and have not taken into account functional impairment. In consequence the lung injury have in principle been assessed qualitatively. Quantitative functional endpoints have only recently been considered as a component of staging system for Late Effects in Normal Tissues (LENT) (Rubin et al, 1995).

The aim of this article is to review the methods of postradiation lung injury evaluation with special reference to functional pulmonary tests.

METHODS OF POSTRADIATION LUNG INJURY ASSESSMENT
Signs and symptoms

Majority of radiation induced lung injuries are asymptomatic. In relatively small proportion of patients, however, dyspnoe,

cough, fullnes in the chest and fever may occur, usually 1-3 months after completion of radiation therapy. Commonly the severity of dyspnoe is scored according to the scale proposed by Mahler (Mahler and Wells, 1988). Some patients, particulary those with severe pneumonitis, may develop symptoms of chronic respiratory failure: exerted dyspnea, reduced exercise tolerance, orthopnoe, cyanosis and, occasionally, chronic cor pulmonale and finger clubbing (Jassem et al, in press).

Radiology

Chest radiography has traditionally been used in evaluation of postradiation pulmonary toxicity. The radiographic abnormalities appear usually 2-3 months after completing radiotherapy and include ground glass opacification, diffuse alveolar or nodular densities, and/or air bronchograms. Occasionally pleural effusion is present (Gross, 1977). Radiation fibrosis usually develops within the previously irradiated field 6-12 months after radiotherapy, irrespective of whether or not the acute syndrome was present earlier. Grading systems to evaluate posttreatment fibrosis take into account the intensity of radiological changes and the involved area (Arriagada et al,1989; Jensens et al, 1985; Massilta et al, 1991).

Recently computed tomography (CT) has been advocated as the method of choice for the radiological assessment of radiation induced lung injury. CT has been reported to demonstrate radiation pneumonitis and fibrosis at earlier stage and with greater sensitivity than classical radiography (Nabawi et al, 1981). Libshitz et al. (Libshitz and Shuman, 1984) proposed four different patterns of CT abnormalities: 1. homogenous, slight increase in density uniformly all over the irradiated area; 2. patchy consolidation within the area, but not confined to the shape of irradiated area; 3. discrete consolidation confined to the shape, but not uniformly involving the irradiated area and 4. solid consolidation confined to and totally covering the irradiated area.

Experimental work of Shioya et al. (Shioya et al, 1990) suggested the role of chest magnetic resonance imaging (MRI) in early

diagnosing of radiation pneumonitis. This technique allows for detection of protein-rich intraalveolar exudate or inflammatory cell infiltrate. MRI may also be of value in distinguishing radiation fibrosis from recurrent tumor (Glazer et al, 1985).

Other imaging technique for the evaluation of radiation lung injury includes 111-In Pentetreotide scanning (Valdes et al, 1996). The usefulness of this test in the diagnosis of radiation-induced pulmonary changes has been demonstrated in our own study (Jassem et al, in press).

Functional tests

One of the goals of classic pulmonary function testing is to determine the type of pulmonary defect in a particular patient. Pulmonary radiation injuries are most frequently of restrictive type with reductions of vital capacity (VC), lung volumes and total lung capacity (TLC). In the combined, obstructive/restrictive type of injury, also forced expiratory volume (FEV) is reduced. Moreover, fibrosis may result in decreasing the airway potency and lung compliance. Finally, there may be an abnormal gas transfer because of alterations in the alveolar-capillary barrier.

Functional tests may evaluate either local or overall lung function. The first group includes nuclear medicine tests and the second - diffusion capacity assay (DLCO) and spirometry.

Nuclear medicine tests

Planar ventilation and perfusion scanning has long been used in assessing post-radiation changes of the lung (Gross, 1977; Prato et al, 1977). Usually the decrease of perfusion is larger than ventilation, thus leading to an increase of ventilation/perfusion ratio (Abratt and Willcox, 1995). The perfusion deficit also seems to precede that of the ventilation. This observation correlates with histological findings showing early damage of the capillary endothelium (Groth et al, 1989). Recently, the utility of single photon emission computed tomography (SPECT) scans in the assessment of post-radiation injuries has been reported (Boersma et al, 1995; Marks et al, 1993). Another useful test evaluating both chemotherapy- and radiation-induced toxicity includes 67-Gallium scanning of the lung. This assay can additionally distinguish radiation pneumonitis from *pneumocistis carini* pneumopathy since the latter is heavily labelled with Gallium (Bisson et al, 1983; Kataoka et al, 1993).

Diffusion capacity assay and spirometry

Some authors have stressed the usefulness of diffusion capacity (DLCO) measurement in evaluating pulmonary changes (Abratt and Willcox, 1995, Mattson et al, 1987). DLCO has been demonstrated to be more sensitive for detection of lung injury than measurements of lung volumes (e.g. forced expiratory volume in one second - FEV1) (Abratt et al, 1990). Decrease of DLCO is a result of radiation damage at the capillary-alveolar level (Law and Ahier, 1989), whereas the changes in FEV1 are related to the balance between direct tissue damage and the traction of adjacent tissue following fibrosis (Choi and Kanarek, 1994).

The role of functional tests

The possible role of functional pulmonary assessment in patients irradiated to the chest includes:
- prediction of lung injury
- diagnosis of lung injury and follow-up after radiotherapy
- grading of lung injury
- monitoring of steroid therapy in patients with symptomatic pneumonitis

Prediction of lung injury

Prediction of postradiation pulmonary function is a difficult and complex task. The primary goal of these attempts is to maximize the radiotherapy dose to the target volume while minimizing normal tissue damage. The predictive value of the individual functional tests for post-therapy lung injury is a matter of controversy (Abratt et al, 1990; Choi, 1990). In order to increase the predictive value of pretherapy assessment, developed were tests including a combination of functional assays. An example of such an approach is coupling quantitative radionuclide perfusion lung scans with spirometry (an adaptation of the model used by thoracic surgeons to estimate the ability of lung cancer patients to tolerate a curative resection) (Brady et al, 1965; Bria et al, 1983; Rubenstein et al, 1988). In this model prospective prediction of the decline in lung function after radiotherapy is calculated with the use of the following formula:

post-treatment FEV1 = pre-treatment FEV1 x (1-fraction of total lung perfusion in irradiated field).

The original study employing this formula included 22 patients administered postoperative or definitive radiotherapy for lung cancer (Rubenstein et al, 1988). The pulmonary

impairment predicted with this method has only rarely been exceeded. Two other studies by Curran et al (Curran et al, 1992) and Choi et al (Choi and Kanarek, 1994) including 210 and 267 irradiated lung cancer patients, respectively, demonstrated only limited predictive power of used formula (table 1).

Table.1

Pulmonary function tests in prediction of lung injury

Author	Malignancy	No. of pts	Tests	Predictive value
Choi (10)	lung cancer	267	Quantitative perfusion and spirometry	Uncertain
Rubenstein (34)	lung cancer	22	Quantitative perfusion and spirometry	Uncertain
Curran (12)	lung cancer	210	Quantitative perfusion and spirometry	Uncertain
Boersma (6)	lymphoma	25	Three-dimensional calculation	Promising

Table 2.

Functional tests after completing radiotherapy

Author	Malignancy	No.	DLCO*	FEV1*	VC*	Qscan*
Boersma (5)	lymphoma	24	19	18	20	10.5
Morgan (28)	breast cancer	17	6	not done	7	not done
Groth (15)	breast cancer	14	8	+5	4	NC
Mattson (27)	lung cancer	34	6	NC	1	NC

DLCO - diffusion capacity, FEV1 - forced expiratory flow for on second, VC - vital capacity, Qscan - perfusion scanning, NC - no change
* % decrease from pretreatment value

In general, this technique tends to overestimate the deleterious effect of irradiation. Additionally, the second study demonstrated that the predictive value of applied formula is dependent on the level of pretreatment FEV1. For values of FEV1>70% the predictive power of the test was acceptable, whereas for FEV1<50% the post-therapy FEV1 was properly predicted in only 10% of patients. Anyway, even with this imperfect method aggressive thoracic irradiation in some patients has been revised by altered arrangement of radiotherapy fields.

An important problem in defining the role of predictive tests in patients with lung cancer given definitive radiotherapy is due to the fact that the final pulmonary function is a result of both: lung injury and improvement related to decreased airflow obstruction following a tumor response. The short survival period of these patients has also added to the difficulties in interpreting the data.

Attempts have been made to correlate the degree of lung injury with radiotherapeutic factors, such as total and fraction dose, fractionation schedule or irradiated volume (Bornstein et al, 1990; Martel et al, 1994; Mattson et al, 1987). Recently adopted three--dimensional (3-D) planning systems enable precise adjustement of the irradition portals to the shape of target volume. Boersma et al. (Boersma et al, 1995) tried to develop a method predicting the reduction of lung function and the probability of developing radiation pneumonitis based on 3-D dose distribution in the lung. In this study the combination of 3-D dose distribution with the average dose-effect relation for local perfusion and ventilation prior to radiotherapy allowed for estimation of the average relative reduction in local lung function. This method also showed a good correlation with the alterations of overall lung functions and appeared to be related to the incidence and severity of radiation pneumonitis (table 1).

Diagnosis and follow-up

Most studies demonstrated no significant alterations of spirometry tests (FEV1 and VC) immediately after completing radiotherapy (Boersma et al, 1995; Groth et al, 1989; Mattson et al 1987; Morgan and Breit, 1995) (table 2). The deepest impairment has been found for DLCO (Mattson et al, 1987; Morgan and Breit, 1995). At the time of presentation of symptomatic radiation pneumonitis generally decline in both diffusion capacity and lung volumes was observed (Jassem et al, 1997; Mattson et al 1987). The highest degree of deterioration, particulary in DLCO, was usually observed after 3 months (Boersma et al 1996; Jassem et al, 1997; Kaufman et al, 1986). In our own material including symptomatic patients, the lowest average value for DLCO at this time was 56.4% of predictive value, as compared with the initial level of 72.7% (Jassem et al, 1997). In the report of Mattson et al. (Mattson et al, 1987), however, the highest decrease of DLCO (by 27%) was noted after 9 months. There are also contradictory data on the spirometry and DLCO pattern with longer follow-up (Boersma et al, 1996; Smith et al, 1989). Boersma et al. (Boersma et al, 1996) observed a partial recovery of local and basic overall lung function, but not DLCO, between 3-4th and 18th month, whereas Smith et al. (Smith et al, 1989) found no significant late impairment of pulmonary function, including DLCO. In our own study including 18 symptomatic radiation pneumonitis patients all applied tests (DLCO, VC, FEV1 and TLC) were worse after 12 months than at the time of radiation pneumonitis diagnosis and FEV1 was at that time the most impaired function (Jassem et al, 1997). Significant decrease in FEV1 after 12 months (from 90.7% to 77.2% of predictive value) in our series might have been due to high incidence of severe fibrosis in this highly selected patient population.

Grading of lung injury

As discussed earlier in this article, most grading systems of pulmonary radiation injury have been purely qualitative. The only exception is recently published LENT system which includes most of the functional tests addressed in this paper. Other graded variables of the LENT sytem are clinical symptoms and signs, radiography and blood tests (Rubin et al, 1995). The value of this system still needs to be verified in clinical setting.

Monitoring of steroid therapy

Administration of corticosteroids is considered a treatment of choice in symptomatic disease. Therapy with these agents in most instances results in a symptomatic relief, but early dose reduction is frequently associated with recurrence of symptoms. Although symptomatic radiation pneumonitis is experienced by only a small proportion of patients given chest irradiation, the troublesome course of this disease as well as the necessity of prolonged corticosteroid therapy dictate the need of better analysis of all concerned factors. No prospective controlled trials on the effectiveness of this therapy, its optimal duration and dosage as well as on treatment monitoring have been performed so far. In the retrospective study including 18 symptomatic patients treated with oral steroids, DLCO values usually maximally decreased at the time of prednisone dose reduction to the level of 15-20 mg (Jassem et al, in press). This alteration has frequently been accompanied by an exacerbation of clinical symptoms. A slight increase of prednisone dose (5-10 mg) usually resulted in symptomatic release and improvement of lung function values. In some patients symptomatic relief has also been achieved with the use of inhaled steroids. The new promising agents include long acting, high dose inhalation compounds, e.g. fluticasene. Recently pentoxiphillin has also been introduced in the treatment of postradiation lung injury (Remiszewski and Roszkowski, 1995). The experience with these forms of therapy have until now been scarce and their role in pulmonary damage warrants further studies. It would be therefore of particular value to include functional tests in evaluation of these novel agents.

CONCLUSIONS

The wide range of functional tests makes possible quantitative assessment of postradiation lung injury. The available data, however, do not yet allow recommendation of any particular assay for the use in standard care. Further evaluation of these methods, including not only their efficacy but also cost effectiveness and availability are warranted.

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