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Role of radiation therapy in lung cancer management – a review

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Abstract. – Lung cancer is the leading cause of cancer death worldwide. Furthermore, more than 50% of lung cancer patients are found affected by distant metastases at the time of diagnosis. On the other hand, 20% of these patients are without regional spread and are good candidates for surgical operation. The remaining 30% represent an intermediate group whose tumors have metastasized up to regional lymph nodes. These remain 30% are the most appropriate candidates for radiation therapy. These patients are also called as "locally advanced lung cancer" or stage III lung cancer patients. In these patients strategy of combination therapy viz. radiation therapy in combination with chemotherapy is also tried by various groups in the recent past for this better management. However, long-term survival is still poor with a 5-year survival in 5-25% of patients. During the last decades, there has been a development in radiation strategies. The present review article focuses on different approaches to optimize radiotherapy for these patients.

Key Words: Radiation therapy, Lung cancer, Metastases.

Introduction

Lung cancer is the leading cause of cancer deaths worldwide. Lung cancer affects each year approximately 1.6 million people globally[1,2]. Furthermore, the incidence is getting more common in the developing countries. Also, female lung cancer patients have shown a significant elevation in the recent past. On the other hand, the incidence is still higher in men. The ultimate well-known causes of lung cancer include primarily the smoking. Secondary factors constitute exposure to radon, arsenic and asbestos.

Lung cancer has been majorly subdivided into two main groups depending upon their histological characteristics and clinical features, namely small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is further divided into various subtypes. Recently, with the help of cytology and immune-histochemical staining methods a new histopathological classification was published[3]. In the lung cancer, despite all the subgroups the most common tumor is the adenocarcinoma or the squamous cell carcinoma. There are many strategies like chemotherapy, targeted therapy, which are followed by the physicians for the efficient management of lung cancer patients depending upon the stage and type of the lung cancer. The present review will be focused on the latest trends in the utilization of radiation therapy in the treatment of lung cancer.

Radiotherapy in Lung Cancer

Radiation therapy has shown a lot of developments in the recent past, especially against lung carcinogenesis. Radiotherapy treatments have proved themselves as an effective treatment option in the standardized dose range of 2 Gy daily to 60 Gy[4]. The highest dose level was superior regarding short-term survival. A Chinese work[5] showed an overall improvement improved in lung cancer patients with the higher dose, implying a dose- response relationship above 60 Gy. There is also an escalation study[6] on hyper-fractionated therapy where the high dose group (69.6 Gy) had a better survival compared to lower dose groups. Apart from these studies data on dose comparisons is sparse. The rapid advancements in the technology allowed feasibility of higher doses ranging from 60-70 Gy in various clinical trials[7-12], where the maximum tolerable dose (MTD) often is limited by doses to the lung. Moreover, it has also been shown that it is safe to escalate the dose with concurrent chemotherapy to 74 Gy[13-15].

Another option to increase radiation efficacy is to utilize altered fractionation. To give doses ranging between <1.8-2 Gy are termed as hyperfractionation, and the doses >2 Gy are collective-

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ly called hypofractionation. If the total treatment time is shorter than for the corresponding time with conventional fractionation (2 Gy daily, once a day, five days a week), it is called accelerated treatment. In comparisons between conventional radiotherapy and hyper-fractionated schedules, higher efficacy has bee observed in the cases utilizing accelerated radiation treatment with more fractionated regimen[16]. There are also indirect data supporting a short overall treatment time as it has been shown that interruption of the radiotherapy course results in decreased survival[17]. Recently there has been a growing interest in hypofractionated strategies, which have been shown to be effective and feasible both per se and with sequential or concurrent chemotherapy[18-20]. Furthermore, a randomized trial of hypofractionated radiotherapy comparing sequential and concurrent chemotherapy had been reported in the recent past where the concurrent arm had a superior survival[21].

Combined radiochemotherapy

The use of two therapeutic modalities namely radiation therapy along with chemotherapy in cancer patients has given rise to the term 'combined radiochemotherapy'. The efficacy of above combination is evidenced in the earlier studies including a meta-analyses review[22,23]. Chemotherapy helped in reduction of risk factors of death of 13% corresponding to an absolute benefit of 4% at 2 years. The working mechanism in this combination could be the reduction of distant metastases. In the above combination, the chemotherapy was initially given in a sequential manner with induction chemotherapy followed by radiation. The next step was to evaluate the addition of chemotherapy concurrently with radiotherapy, as it was known that cytotoxic agents had the possibility to enhance radiation because of their radio-sensitizing effects that will be discussed in the later section of this review.

A few studies compared concurrent chemo-radiotherapy with radiotherapy alone[24-26] and the superiority of chemotherapy in this setting resulted in an absolute survival gain of 4% at two years[26]. Later on, some trials comparing the sequential versus the concurrent approach were made, where the concurrent schedules showed higher efficacy and survival due to improved local control[28,29]. The superiority of concurrent schedules with significantly improved survival over sequential has been confirmed in a systemic review[30].

The concurrent chemotherapy can be administered as full dose courses or as low dose on a weekly or daily basis. In theory, the latter is enhancing the radiation effect, thereby, improving local control whereas the former should have a higher possibility to eradicate micrometastatic disease. There are no direct comparisons between these two treatment strategies, but as distant metastases is a considerable problem and it has been shown that the metastatic frequency can be lowered with induction chemotherapy, some would argue that just delivering radio potentiating low-dose treatment without induction will not be enough and that data implied that schedules with full dose chemotherapy tend to have somewhat higher survival figures. Concurrent chemotherapy has also been shown to be feasible in hyperfractionated accelerated schedules[31]. In dose escalation studies and recently, concurrent chemotherapy has been reported to be feasible and superior to sequential therapy in hypofractionated treatment[32].

Radio-Sensitizing Mechanisms

The rationale for combining a pharmaceutical agent with radiation is the possibility of achieving a synergistic effect. The use of radiation therapy with chemotherapeutic pharmaceutical improvised treatment by various mechanisms including inhibition of repair of radiation-induced damage, reduced repopulation, increased apoptosis and increased re-oxygenation, thereby making the tumor cells more sensitive to irradiation. The cytotoxic agents that are combined mostly with radiation are cisplatin, carboplatin, paclitaxel, docetaxel, etoposide and cetuximab. Cisplatin, as well as carboplatin, are alkylating agents that crosslink the DNA strands leading to DNA breakage during replication and cisplatin too can cause DNA strand breaks directly. Both of these drugs are not cell-cycle specific but are able to induce DNA strand breaks and crosslinks in any phase of the cell cycle but S phase is favorite target. They both believed to inhibit repair of radiation-induced damage have been shown to stimulate the number of radiation-induced strand breaks. On the other hand drugs like taxanes paclitaxel and docetaxel mainly act by stabilizing the mitotic spindle apparatus leading to death in the mitotic cell or accumulation of the cells in the G2/M phase where the cells are very sensitive to radiation. Etoposide is a topoisomerase inhibitor, arresting the cells in S → early G2 phase in the cell cycle, and the interaction effect with radiation is probably due to im-

paired repair and apoptosis. Finally, the antibody cetuximab acts by binding to the epidermal growth factor receptor and, thereby, prevented ligand-induced phosphorylation, which in turn cause stimulation of receptor endocytosis and degradation. A strong synergistic growth inhibition has been observed in cell lines together with radiotherapy, which is the result of inhibition of DNA damage repair [33,34].

Choice of Chemotherapy

In earlier trials, the use of a single chemotherapeutic agent, especially a platinum-based drug, was the choice of chemotherapy to be integrated into the irradiation schedule[35]. Later investigations on the "third generation" cytotoxics with combinations of platinum plus either of gemcitabine, paclitaxel or docetaxel showed an improved efficacy compared to single platinum-based chemotherapeutic agent[36]. A study in a recent past[37] has proved that doublet is more effective than a single chemo agent. Hence, the standard therapy usually is a platinum doublet, cis- or carboplatin with one of the "third generation" cytotoxic agent, which usually include paclitaxel, docetaxel and gemcitabine[38]. Vinorelbine is another effective drug with robust long-term supportive data in the adjuvant setting[39]. On the other hand, cisplatin plus docetaxel have shown higher efficacy than cisplatin/vinorelbine in a study in stage IV disease[40]. There is no consensus regarding the second drug, probably paclitaxel, docetaxel, gemcitabine and vinorelbine have comparable efficacy. However, one important issue is that the compound needs to be able to integrate well with radiotherapy without excessive toxicity, which for example is seen with gemcitabine. Therefore, the most common combinations are cis- or carboplatin together with paclitaxel, docetaxel or vinorelbine. When it comes to the choice between cisplatin and carboplatin there are no direct comparisons. However, a meta-analysis in stage IV disease showed cisplatin to be more effective when combined with a third generation drugs[41]. Furthermore, cisplatin is superior in the adjuvant setting with regard to long-term survival[42]. Nevertheless, when considering available data, cisplatin is the drug, which is recommended in regimens with curative intent in fit patients both in the adjuvant postoperative setting and in combination with radiotherapy.

Recent Advances in Radiation Therapy

Consolidation Therapy

Consolidation therapy is an option for the later stages of lung cancer disease, where target specific drugs like pemetrexed and erlotinib have been used in combination with radiation treatment and have shown increased survival[43,44]. So far there are no trials showing a benefit of consolidation therapy after full dose radiochemotherapy in stage III disease, but there are reports on feasibility regarding docetaxel[45] and docetaxel/carboplatin[46]. Moreover, gefitinib has been evaluated in a randomized manner but it had a detrimental effect with the placebo arm showing a significant superior survival[47]. This was probably due to tumor progression in the gefitinib arm and not because of toxicity.

Prophylactic Cranial Irradiation

As a high proportion of the patients developed brain metastases, several attempts have been made to find out whether prophylactic cranial irradiation (PCI) would be beneficial. Almost all of the randomized trials showed a delay in occurrence and/or reduction of brain metastases but no survival advantage. To resolve this question, RTOG-0214 was launched being powered to detect a survival difference. Unfortunately, it closed prematurely due to slow accrual, and did not meet its primary endpoint, but as the other trials, it showed a reduction of brain metastases but no significant impact on survival[48].

Conclusions

Today's standard treatment of lung cancer in advanced stages is concurrent chemoradiotherapy to 60-70 Gy. The chemotherapy should be a platinum-based doublet but there is no more precise consensus about the choice of drugs. Furthermore, there is no consensus regarding high dose or low dose chemotherapy. Accelerated regimens are considered more effective than conventional fractionation but have at most centers not been routinely introduced, probably due to uncertainty about concurrent chemotherapy and for practical reasons. Adding targeted therapies to radiation, using consolidation therapies, further increments in the radiation doses and hypofractionated schedules are all topics for future investigation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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