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IAEA clinical guidelines

Lung cancer management in limited resource settings: Guidelines for appropriate good care

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Abstract

Lung cancer is a major cause of cancer death worldwide and is becoming an increasing problem in developing countries. It is important that, in countries where health care resources are limited, these resources are used most effectively and cost-effectively. The authors, with the support of the International Atomic Energy Agency, drew on existing evidence-based clinical guidelines, published systematic reviews and meta-analyses, as well as recent research publications, to summarise the current evidence and to make broad recommendations on the non-surgical treatment of patients with lung cancer. Tables were constructed which summarise the different treatment options for specific groups of patients, the increase in resource use for and the likely additional clinical benefit from each option. These tables can be used to assess the cost-effectiveness and appropriateness of different interventions in a particular health care system and to develop local clinical guidelines.
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Lung cancer is the most common cancer globally with, in 2002, 1.35 million new cases *per annum*, or 12.4% of all new cancers [39]. It is also the most common cause of death from cancer, with 1.18 million deaths, or 17.6% of the total [39]. We have already seen a geographical shift in incidence because of changing patterns of tobacco use in the developing world. In 1980 the proportion of lung cancer in the developing world was 31%, but in 2002 this had risen to 50%, a trend which is set to continue [16].

Developing countries have markedly fewer resources than the developed world. The richest 20% of the world's population uses 83% of the world's resources while the poorest 60% of the population only uses 5% [54]. Even in developed countries, resources may be unevenly distributed, with relative lack of resources in some communities. For instance, the acquisition of megavoltage equipment per unit of population (100,000 people) is proportional to a country's per capita gross national income, resulting in less per capita availability of such equipment in poorer countries [29]. Therefore, many cancer patients will not have access to treatments which are standard elsewhere. The importance of radiotherapy in treating cancers, including lung cancer, in developing countries has recently been highlighted [7].

This document has been prepared by a technical group organised and coordinated by the International Atomic Energy Agency (IAEA). Its aim is to help oncologists who care for lung cancer patients in limited-resource settings as they formulate their own local guidelines. We hope that it will make it easier to estimate the cost-effectiveness of treatments which require more resources than those of the baseline reference regimens. Decisions about local priorities can then be made on the basis of evidence, rather than on personal bias, fashionable practice or the influence of commercial interests. The document may also help oncologists working where resources are limited to lobby for better resources.

A minimum baseline of personnel, organisation, associated services (e.g. pathology and diagnostic radiology) and specialised equipment is required for the safe practice and development of oncology services. Although the appropriate treatment of all lung cancer patients should be considered whatever the resources available, management where the facilities are below a basic threshold is outside the scope of this paper. We consider a baseline level of non-surgical treatment facilities to be at least cobalt megavoltage therapy with two-dimensional planning and outpatient chemotherapy with conventional agents.

We have tried to identify baseline reference treatment regimens, which can be delivered by an oncology service with access to these basic resources, and then to describe the incremental resources needed, as well as the risks and

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benefits to the patients of more sophisticated, and often more intensive therapy. We have not tried to cost these different therapeutic options; costs will vary depending on such factors as international exchange rates and salaries. Capital equipment and drugs are often relatively expensive in developing countries, because these are at international rates, while salaries will be at local rates and less costly.

A difficulty, which we freely acknowledge, is that almost all the research, especially that involving new techniques, equipment and drugs, has been carried out in countries where resources are generally not limited. Therefore the interpretation and application of this evidence have to be based on judgements about the transference of treatment techniques to other situations.

Guidelines are not prescriptive and should not be used to replace clinical experience and judgement. Individual patient evaluation is a very important part of lung cancer treatment, and clinical decisions must always take into account the patient's fitness for treatment, their performance status (PS) and the presence of co-morbidities.

Methods

The authors met for a two-day consultant meeting at the IAEA (March 9—10, 2006) during which the methods of working were agreed, and the main approaches were drafted. Reference was made to recent English language clinical guidelines [6,36,40,52] which included robust and systematic reviews of the research evidence. This evidence was supplemented by other recent systematic reviews, meta-analyses and research. Following the meeting drafts were circulated sequentially around the group members.

We have assumed that adequate pathological and diagnostic resources are available to enable patients to be grouped according to histology and stage.

Small cell lung cancer (SCLC)

Patients with SCLC are divided into those with limited disease (LD), usually defined as 'disease that is confined to a hemithorax and regional nodes that can be encompassed in a reasonable radiation port' [52], and those with extensive disease (ED). The minimum diagnostic tests to establish stage are clinical examination, chest X-ray, liver function tests and liver ultrasound (US). If these show that the patient has extensive disease, there is no justification for a CT scan. However, CT of the chest and upper abdomen is a more accurate method of determining the disease extent, if easily available. Isotope bone scan and CT (or MRI) of brain should only be used if there are clinical indications. It may be useful to use the above results, as well as those of the assessment of performance status (PS), serum sodium and lactate dehydrogenase (LDH), to assess the patient's likely prognosis using a recognised prognostic score [12]. Intensive potentially curative treatment should only be considered for patients found to have a good prognostic score.

Limited disease SCLC

SCLC is chemo-sensitive. In 1978 the use of combination chemotherapy with cyclophosphamide, doxorubicin and vincristine for patients with limited SCLC resulted, historically, in a response rate of 75% and an increase in survival, compared to untreated patients, from 3 to 12 months [30].

The current reference regimen is cisplatin and etoposide (PE) which is highly active in patients with SCLC. A trial comparing PE to a non-platinum combination regimen, in patients with both limited and extensive disease, found an increase in median survival from 9.7 to 14.5 months ($p = 0.001$) and a 12% increase in absolute survival with the cisplatin containing regimen at 2 years [55]. A meta-analysis has shown that improvement with cisplatin, in patients with both LD and ED, is independent of the administration of etoposide with an increase in 1 year survival of 4.4%, an odds ratio (OR) of 0.8 and $p = 0.002$ [46].

Consolidation radiotherapy to the chest, given after chemotherapy, has been shown to further improve survival rates in patients with LD SCLC. A meta-analysis showed a 14% reduction in death rate ($p = 0.001$), a relatively larger reduction in younger compared to older patients. The absolute survival benefit was 5.4% at 3 years. [41,42]. Chest radiotherapy can be given as parallel opposed AP/PA fields planned on a simulator, treating the mediastinum and site of tumour with regimens such as 40 Gy in 15 fractions, 45 Gy in 18 fractions or 54 Gy in 27 fractions with dose reduction to the spinal cord, either by use of oblique fields or spinal cord shielding for two or three fractions.

In the past consolidation chest radiotherapy was always given following four or six cycles of chemotherapy. More recently trials have investigated the use of radiotherapy given concurrently with chemotherapy and have consistently reported an increase in the rate of severe oesophagitis with concurrent treatment, especially if anthracycline chemotherapy is given. The timing of radiotherapy in these schedules has also been investigated. Three meta-analyses and systematic reviews on this topic have been published, two of which [18,23] have shown a survival advantage for the early administration of combined radio-chemotherapy, while the third one [14] did not. Current consensus favours the use of concurrent chemo-radiotherapy schedules in which the radiotherapy is given early.

A twice daily, hyperfractionated accelerated chemo-radiotherapy schedule, with 45 Gy given in 30 fractions over 3 weeks, has also been shown to increase overall survival [59], but this comes with a number of cost and practical issues, as well as a significant further increase in oesophagitis. It is not clear whether the benefit in this trial came from the twice daily regimen itself or because the radiotherapy was accelerated and given over a shorter period than in the very prolonged comparator regimen of 45 Gy in 25 daily fractions over 5 weeks. One systematic review [14] has indicated that better outcomes are associated with a shorter overall treatment time.

Prophylactic cranial irradiation (PCI) following chemotherapy benefits patients with LD SCLC who have had a complete response (CR) to chemotherapy [3,4]. A meta-analysis has shown a reduction in the risk of death of 16% with PCI, which corresponds to a 5.4% increase in survival at 3 years (15.3% in the control compared to 20.7% in the treatment group) [4]. Doses of between 24 and 30 Gy in 2 Gy fractions may be used. Although there is no clear evidence of radiation-induced late neurotoxicity