Brain metastases are the most feared complication in the systemic progression of neoplastic disease, and the most frequent brain 'tumours', with an incidence 10 times higher than primary lesions. Autopsic studies have shown that the neoplasms with the highest incidence of brain metastases, in order of decreasing frequency, are the lung, breast, kidney and colon [1].

Lung neoplasms are the most common cause of cancer-related death. There are expected to be more than 165 000 new cases of primary lung cancer in the USA in 2006, and in 25–40% of these patients the disease will progress and involve the brain. Moreover, their longer survival thanks to better treatment in the early and advanced stages will probably also affect the frequency of brain metastases. Already at diagnosis, 10% of non-small cell lung cancer (NSCLC) cases have brain involvement, 6–9% of radically-treated NSCLC recur only in the brain and, as mentioned earlier, 25–40% of patients develop metachronous brain metastases. The prognosis is extremely dismal: patients given supportive therapy alone have a life expectancy of approximately 1 month [2]. After radiotherapy, patients survive approximately 5 months and 10% of patients are still alive about a year.

The treatment options for patients with brain metastases from NSCLC are illustrated in Table 1.

Factors influencing the choice of treatment include age, Karnoński performance score, any extracranial metastases at diagnosis, and the number, site and size of the metastases.

A review of the databases on 1200 patients recruited between 1979 and 1993 and enrolled in three consecutive RTOG trials [3] enabled patients to be classified on the basis of three variables that proved statistically significant: PS, age and local control of the primary tumor. Using this classification enables a comparison of the outcome and efficacy of new therapies in homogeneous groups (Table 2).

Whole brain radiation therapy (WBRT) has always been considered the treatment of choice for brain metastases because it prolongs the mean survival rate from 1 to 6 months [4].

The rationale for WBRT lies in that radiotherapy affords a good local control, eliminates any micrometastases, reduces the risk of recurrent brain metastases, improves overall survival and quality of life, and can prevent death due to brain compression syndrome [5]. WBRT is also a widespread, easily implemented, non-invasive technique.

The treatment is generally hypofractionated, administering 30 Gy in 10 fractions [6]. The drawbacks of WBRT are that its effect on large lesions is limited, the local control rate is less than 50%, 25–50% of patients fail to respond to the RTE and late toxicity can be severe in any long-term survivors [7].

Among the new treatment options, apart from surgery, the last 20 years have seen the introduction of stereotactic radiosurgery (SRS) in clinical practice [6]. SRS enables a highly-focused distribution of large doses in single fractions. The first case of γ-Knife (GK-SRS) treatment of a brain metastasis was reported in 1975. What makes the metastasis an ideal target for this type of treatment is its spherical shape, clear distinction from the adjacent tissue on imaging and dimensions no more than 3 cm.

The advantages of SRS over surgery include a brief or no hospital stay, scarce invasiveness, low complication rate (4%), and low cost. In addition, the dose drops rapidly beyond the target volume, inducing minimal changes in the surrounding brain tissue. The availability of modified linear accelerators for performing radiosurgery, sometimes integrated with the

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**Table 1.** Therapeutic options

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Whole brain radiation therapy (WBRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery ± WBRT</td>
<td></td>
</tr>
<tr>
<td>Surgery ± localized radiotherapy</td>
<td></td>
</tr>
<tr>
<td>WBRT ± radiosensitizers</td>
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<tr>
<td>WBRT + chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Radiosurgery (SRS) ± WBRT</td>
<td></td>
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<td>Chemotherapy alone</td>
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</tbody>
</table>

**Table 2.** RPA class and median survival

<table>
<thead>
<tr>
<th>Class</th>
<th>KPS ≥70; age &lt;65; controlled primary; no extracranial disease</th>
<th>Median survival: 7.1 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 2</td>
<td>All others</td>
<td>Median survival: 4.2 months</td>
</tr>
<tr>
<td>Class 3</td>
<td>KPS &lt;60</td>
<td>Median survival: 2.3 months</td>
</tr>
</tbody>
</table>
micro-multileaf collimator, has enabled the method to be adopted at numerous radiotherapy centers. The disadvantages of radiosurgery lie in the need for an accurate patient selection and in that few centers in Italy currently have the necessary γ-Knife, Cyber-Knife or modified linear accelerator equipment.

In a study in 2001 on 238 patients treated with GK-SRS alone or after WBRT had failed, Stripp [8] reported local disease control in 97% of cases and confirmed the effectiveness of aggressive treatment for these patients, identifying age, initial number of lesions and Karnofsky performance score as prognostic factors.

In a retrospective study on 72 patients who had GK-SRS alone or in association with WBRT, Flannery et al. [9] found that, in 45 cases, in addition to the prognostic factors known to be statistically significant on uni- and multi-variate analysis, there is also the presence of a metachronous rather than a synchronous single metastasis: this factor affords a mean survival advantage (33.3 months vs. 8.6). Adjunctive WBRT does not improve the OS achieved by SRS alone.

In another retrospective study on 113 patients, Hoffman et al. [10] found that combined SRS-WBRT treatment improved local control in patients with positive prognostic factors, extending their disease-free interval, but not their overall survival.

From 1987 to 2002, the Oncological Radiotherapy Unit in Treviso treated 491 patients with brain metastases from lung primaries using a conventional WBRT regimen of 3000 cGy in 10 fractions. Mean survival was 4.8 months.

The prospective assessment of the role of SRS plus WBRT versus WBRT alone in the treatment of multiple brain metastases currently demonstrates that the combined treatment is effective in terms of both local control and a better QoL, but achieves no improvement in overall survival.

These results have also been confirmed by the randomized study conducted by the RTOG, which failed to obtain, any significant improvement in survival (5.7 vs. 6.5 months) in patients with up to 3 metastases, while results were better for patients with a single metastasis (4.9 vs. 6.5 months) [11].

In recent years, research has continued to focus on new chemo-radiotherapeutic strategies with a view to improving the very poor prognosis for patients suffering from brain metastases from NSCLC. Despite the introduction of new equipment and new fractionation methods, WBRT remains the standard treatment both for its efficacy and for its ease of implementation. SRS is indicated for selected patients, but its association with WBRT offers no improvement in overall survival. Experiments are currently being conducted with radiotherapies administered sequentially or in concomitance with chemotherapy and ‘target-therapy’ drugs.

references