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Refresher course: oligometastases

Oligometastatic cancer: A curable disease stage

Larrea Rabassa, Luis Maria

Hospital NISA Virgen del Consuelo, Director del Servicio de Oncología Radioterápica, Spain

The word metastasis is originally a Greek word meaning "displacement", from *meta*, "next" and *stasiç*, statis, "placement".

Cancer treatment and survival are determined, mainly, by whether or not a cancer remains localized or spreads to other locations in the body. Cancer staging describes the extent of the tumor and it is critical because treatment is based on this parameter. Staging systems for cancer have evolved over time and continue to do so. The universally accepted staging system for solid tumors (except for those located in the central nervous system) is that of the UICC (and AJCC) based on the TNM system, initially developed by Pierre Denoix between 1943 and 1952). TNM combinations correspond to one of five stages: Stage 0 for in situ, Stages I–III for loco-regional disease and Stage IV for metastatic disease.

The "N" category defines localized spreading to regional lymph nodes near the primary tumor and is not normally counted as metastasis, although distant metastatic ocurrences worsens the prognosis. In stage IV there is evidence of distant metastases (M1) and traditionally was associated with a 0% long term survival (not curable). Although diseases arise in nature, their diagnostic categories are generated by man in ways that are useful, so this classification is occasionally suffering modifications and has exceptions to adjust to modern data that are arising from the new treatments. Currently, for example, supraclavicular lymph node spread is not considered now a metastasis (it's considered a N3 disease) and metastatic thyroid papillary carcinomas are not necessarily stage IV anymore.

The traditional concept of incurability of stage IV, and the idea that metastatic patients have terminal disease is changing. In 1995, Hellman and Weischselbaum proposed a paradigm shift, introducing the notion of "oligometastases". They hypothesize that in some patients with a limited number of clinically detectable metastatic tumors, the extent of disease exists in a transitional state between localized and widespread disease.

There is evidence suggesting that local control of oligometastases may yield improved systemic control and prolong disease-free survival. Improvement in local therapies such as surgery, radiotherapy or radiofrequency ablation for the oligometastatic sites could thus improve patient's survival.

Arguments to support oligometastatic as a different clinical stage (maybe M0, M1 for one metastasis, M2 for oligometastatic and M3 disseminated with no possibility for local control, or IVA vs IVB?) could include:

- Curative intent-treatments are possible
- Few lesions with usually poor growth capacity
- Reflects cancer cells with limited metastatic capability or limited by chemotherapy systemic treatment
- Is the early detection of a potentially larger disease

However, there are also questions to be solved in the oligometastaic setting:

Should there be an operational max number cut-off point? (for example: less than 5 or 8 macroscopic lesions) Or consider the number and the total volume?

- Should there be an operational max metastatic volume cut-off point?
- What is the real prevalence of oligometastatic disease? Does it depend on the quality and type of diagnostic explorations done?
- Does their outcome depend on their early diagnosis?
- Is there indication to treat all metastasis simultaneously or some do have priority?
- Which is the most convenient follow-up?
- Are there any prognostic or risk factors?
- What's the biology of all this? Given that there's no randomized/universal seeding and there appears to be some target tissue (soil) interaction/local growth factors. The dormancy and abscopal effects sometimes observed have not been

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clearly explained, genetic instability of the primary and the metastatic tumors might be taken into account. Anatomic and mechanic factors (cascade/step by step dissemination) also appear to play a role...

Current data shows that oligometastatic patients are a very heterogeneous group and that there are not enough reports on their long term follow-up. Local treatments less invasive than surgery seem to be gaining a place. Undoubtedly, this particular clinical situation would benefit from a multidisciplinary approach.

Oligometastases treatment examples in use and with proven results include:

- Resection of liver metastases in colon tumors (with or without previous chemotherapy for cito-reduction and resectability improvement)
- Resection or SBRT of lung metastases from multiple primaries
- Adrenal gland resection in lung tumors
- Brain metastases surgery or radiosurgery
- Solitary bone metastases SBRT.

The mayor relevance for oligometastasis is the better local treatments as there are improving radiotherapy techniques, first with radiosurgery for multiple brain metastasis and later with SBRT for systemic metastasis, mainly lung, spinal and liver. As previous historic improvement in surgery development for better results, also radiotherapy improvements modify treatment with better local control and prognosis for oligometastatic patients.

It is not the same the prognostic for a breast cancer patient triple negative with oligometastatic brain metastasis or with Her2 positivity. The SBRT treatment for oligometastatic lung metastasis has nearly 100% local control, but which patients will improve survival and quality of life?

The paradigm is always how to classify the oligometastatic patients and how to decide the always necessary multidisciplinary treatment.