



Pulmonary metastasectomy in germ cell tumors and prostate cancer

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Abstract: Pulmonary oligo-metastases and oligo-recurrences are terms used to define a set of clinical conditions consisting of limited metastatic malignant disease characterized by an intermediate aggressive behavior compared to diffuse metastatic conditions. If the primary tumor has been controlled and extra-thoracic lesions are excluded, there is a suggestion in the medical literature that removal of such lesions could potentially prolong survival. The lungs are a common metastatic spreading site, especially from epithelial malignancies and sarcomas; pulmonary surgical or interventional metastasectomy have been proposed with curative intent in case of limited tumor load (usually less than 5 lesions). There are many series reporting data about colorectal, renal or breast lung metastasectomy, but the absence of multi centric prospective trials determines a lack of definitive evidence, especially for less common tumors such as metastatic germ cell and prostate cancer. They rarely present in the oligo-metastatic form and their management is often based on personal experience. The aim of our article is to review the latest evidence in the treatment of pulmonary metastatic germ cell and prostate tumors. We cover the full range of treatments: from surgery to ablative radiotherapy and combination of local and systemic therapy. Despite the absence of evidence based guidelines, it emerges that pulmonary metastasectomy should always be considered when general criteria for resection have been met. In germ cell tumors surgery should be mainly reserved for residual disease after chemotherapy, whereas in prostate cancer, pulmonary metastasectomy should be preferred to avoid or delay hormonal deprivation therapy and its side effects.

Keywords: Metastasectomy; pulmonary; germ cell tumor; prostate cancer

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Introduction

Metastatic cancer is usually associated with aggressive behavior with poor prognosis and, usually, patients are referred for palliative treatments. In case of oligo-metastatic stage, that is a limited number of metastatic lesions, it might be appropriate to postulate a less aggressive behavior with better outcomes (1). In these, selected sub-group surgery

is progressively assuming the new role of potential curative treatment, if all sites of metastasis could be controlled.

In 1997, a long-term prognostic analysis on 5,206 lung metastasectomies showed that survival after complete resection was 36%, 26% and 22% at 5, 10 and 15 years respectively with a median survival of 35 months. Based on these results, surgical resection for pulmonary metastasis has been commonly introduced in thoracic surgery.

According to the International Registry of Lung Metastasis report, the most represented histology is epithelial (43%) and sarcomatoid (42%) tumors, whereas germ cell and malignant melanoma are respectively 7% and 6% of the other cases.

Since each histological type behaves differently, it is reasonable to assume that the efficacy and role of surgery depend on the primary tumor histology. Specifically, PM impact on survival in advanced germs cells and prostate tumors is still unclear and the absence of updated evidence-based guidelines often determines their management to rely on personal experience only. In 2019, the Society of Thoracic Surgeons (STS) Work Force of Evidence Based Surgery established a panel including experts in thoracic surgery, medical, and radiation oncology, in order to develop an STS expert consensus on PM (2). They decided that some general criteria should be always observed before referring patients to metastasectomy. The most important are: (I) primary cancer control, (II) absence of other extra-thoracic metastasis and (III) complete metastasis resection. In addition LN involvement, DFI, number of metastasis and laterality are also influencing points (3). Building up on these basic rules, we will deal specifically with germ cell and prostate tumor metastasis.

Germ cell tumors (GCTs)

GCTs are malignancies originating from reproductive cells with either malignant or benign behavior. Germ cells are usually found in the gonads (ovaries and testis). However, they can also be located in other parts of the body (such as: pineal gland, brain, mediastinum, or abdomen) in case of birth defects resulting from errors during development.

GCTs are histologically classified in two types, regardless of body location. There are the germinomas germ-cell tumors (GGCT), that includes only germinoma and the non-germinomas germ-cell tumors (NGGCT) including all others.

This classification is based on their clinical behavior. On one hand, NGGCTs are more likely to grow fast, affect younger patients, and present a lower 5-year survival rate. NGGCTs comprehend embryonal carcinoma, teratocarcinoma, choriocarcinoma and yolk sac tumors. These are characterized by a strong propensity to disseminate, especially to the lungs (4). On the other hand, germinomas tumors present a better survival rate due to their intrinsic sensitivity to radiation and chemotherapy.

Testicular carcinoma is the most frequent malignant

disease in young people aged between 15- and 35-year-old (5). Careful staging, timely systemic therapy and strict follow-up represent key points for successful outcomes. Unfortunately, though, metastatic spreading is possible even in early stages with about 8% of stage I cases developing lung metastases.

In advanced disease, lung, liver, brain and bones are the most common sites of spreading. Metastases can occur as late recurrences after a disease-free interval (DFI) or as chemotherapy-resistant synchronous disease. Their management is based on combination of chemotherapy and radiotherapy whilst surgery should be considered only for residual disease.

Tumor re-staging is performed by PET scan in association with serum tumor markers measurement (STMs). At present, available STMs are alpha-fetoprotein and beta-human chorionic gonadotropin. They are used during diagnosis but also in the management of advanced disease. Indeed, response to chemotherapy should be confirmed by imaging and STMs reduction. Nevertheless, in spite of the fact that about 54% to 71% of cases with residual disease and STMs normalization have complete necrosis or fibrosis in residual pulmonary masses (6), those could be composed by undifferentiated tumor with viable cancer, even with normal STMs.

In light of those considerations, the introduction of a multimodality approach (chemotherapy with surgery) in the management of advanced disease improved 5-year survival from 30% in the 1960s to 90% from early 1980s (7).

Surgery

Metastasectomy, with particular references to pulmonary metastasis, has been introduced from the early 1970s. It should be reserved to patients who present residual disease after chemotherapy. Indeed, chemotherapy is the gold standard also for advanced cases and achieves the best outcomes. However about 20–30% of subjects whose undergo systemic therapy for germ cell metastasis present residual disease (8,9).

Outcomes after PM in germ cell tumors in terms of survival are very encouraging with a 5-year OS ranging from 42% to 95% (10–12), but results are strictly conditioned by selection criteria. These are obviously consistent with general criteria for PM (complete resection, control of primary tumor, absence of extra-thoracic disease, long DFI) with some more peculiarities due to tumor histology.

According to the European Germ Cell Cancer

Consensus Group (EGCCCG) PM is recommended after completed standard chemotherapy with cisplatin and serum markers normalization (13). Metastasectomy is, traditionally therefore, reserved for completion therapy for residual thoracic disease, in a multimodality fashion.

Further indications have been proposed over time broadening this practice. Different authors advocate pulmonary metastasectomy also in case of partial or absence of response to chemotherapy with palliative purpose in case of large necrotic or infected tumors or with diagnostic purpose when tumor nature needed to be confirmed or when viable tumor should be identified (14). Multiple pulmonary metastases, persistent elevated STMs or repeated PM have not been excluded either (15,16). Furthermore, despite some articles reported better outcomes in case of single metastasis, there is no evidence that the number of nodules negatively affect prognosis.

Similarly, bilateral disease should not be a contraindication either. Indeed, several authors have shown that tumor histology is often different in the two lungs, confirming the need of bilateral approach to achieve radicality (12,17).

Generally speaking, PM must be performed as soon as possible after diagnosis. In GCTs, since chemotherapy is the gold standard, surgery should be instead planned after systemic therapy. In order to avoid or reduce chemotherapy-induced complications, it has been suggested a rest time of 3–6 weeks (17–19).

Correct surgical approach for PM in GCTs is unclear, since most of available studies are focused on PM in general. VATS advantages are less postoperative pain and earlier patient recovery, whereas open surgery allows parenchymal bi-manual palpation with even small nodule detection (18,20). In favor of VATS, Margaritora *et al.* (21) have pointed out that modern CT scan provides nodule detection even in 6 mm lesions making manual palpation often not useful or even less effective. At the same, Boffa *et al.* (18) showed that GCTs lung metastasis are often peripheral and small, suggesting successful parenchyma evaluation with VATS as well.

Open surgery is probably more frequent, as reported by Farazdaghi *et al.* (22), in a review of 12 papers between 1990 and 2018 where 84% of procedures were performed by thoracotomy, 13% by sternotomy, 3% by clamshell approach and only 1% by VATS.

In spite of the approach, pulmonary wedge resection is the most common procedure for metastasis excision with a percentage of about 77% in metastatic GCTs (22). This

approach is preferred because allows parenchyma sparing, particularly useful when concomitant or future additional resections must be taken into account. Even more so since there is no evidence that anatomical resection improves outcomes over non-anatomical ones (23,24).

Radicality of surgery (i.e., R0 resection) is strictly linked to survival in GCTs. Pfannschmidt *et al.* in 2010 (25), showed a survival improvement from 28.6% to 80.9% in patients with incomplete and complete resection and suggested that nodules until 0.3 cm should be removed (19,21,26).

Usually, 0.5–1.0 cm is considered the optimal margin (27) for metastasectomy, however some authors have suggested wider normal lung tissue surrounding the nodule (2,28). These criteria should be applied also for GCTs.

Lastly, nodal dissection role is still uncertain, but many series reported cases of mediastinal nodes involvement, suggesting that removal should be always considered (12,22,29,30).

PM for GCTs is safe with low morbidity and 30 days mortality ranging from 0.0% to 3.6% (10,23,25). These data are consistent with PM in general. However, GCT patients are more likely to develop complications, since surgery is performed at the end of a chemotherapy regimen. In particular, since some regimens present higher lung toxicity, pulmonary complications are frequent. The most common pulmonary complications are ARDS, pneumonia, prolonged air leaks and prolonged respiratory failure requiring mechanical ventilation. Non-pulmonary complications are atrial fibrillation, sepsis and acute kidney failure.

Therefore, it is recommended to manage chemotherapy with a view to following surgery. In particular, patients treated with bleomycin seem to be more likely to develop respiratory complications due to lung toxicity (31,32). Therefore, currently regimens consisting of etoposide, ifosfamide and cisplatin (VIP) are preferred to historical combination of bleomycin, etoposide and cisplatin (BEP) (33).

PM for GCTs is successful if part of a multidisciplinary approach based on chemotherapy as first treatment. According to recent literature, 5 years overall survival after PM ranges between 73% and 94% (10,12,25,30) with a median survival of 5.6 years in case of salvage surgery (23). These data confirm the significant improvement obtained with multimodal therapy over previous decades when survival ranged between 59% and 82%.

To conclude, multimodal management is mandatory and PM for residual pulmonary disease after chemotherapy should be always considered. R0 must be achieved.

Prognosis is determined by histology; if nodules resected result necrosis, fibrosis or mature teratoma, outcomes are favorable. On the contrary, when residual malignant cells are detected, outcomes worsen. Unfortunately, definitive diagnosis of necrosis, teratoma or viable cancer in lung nodules can be obtained only by pathology. Lastly, salvage surgery might have a role since it could prolong survival, despite being associated with ultimate adverse prognosis (10,25,30).

Non-surgical management

SABR, stereotactic ablative radiotherapy, is an emerging treatment for pulmonary tumors. One of the most intriguing topics in these years is its role in the management of stage I NSCLC. At the moment, based on encouraging outcomes, it is common opinion that SABR is an established option in patients who refuse or are not fitting for surgery (34). In the same way, many authors support its attractiveness for the treatment of pulmonary oligo-metastases (35).

The role of SABR in oligo-metastatic patients is to achieve complete or partial tumor control due to its established efficacy with low side-effects incidence. Many papers report 1-year disease local control ranging between 70% and 95% of cases (35-38). At the same time, some prognostic factors have been identified. Among these, the most influencing outcomes are number of metastases, size of pulmonary nodules, number of organs involved and duration of disease interval free period.

All published series concerning SABR in oligo-metastatic patients include different epithelial tumors and no evidence support that histology could be a significant prognostic factor (39,40). Numbers of nodules, tumor dimension and DFI are the only prognostic factors with an evidence. It has been shown that prognosis is better when nodules are 5 cm or less and smaller than 3.3 cm in size, and DFI is longer than 3 years.

Evaluating the role of SABR in pulmonary germ cell tumors metastasis, the only available data come from previous retrospective trials without tumor specificity and based on heterogeneous groups of primary malignancies. Moreover, despite encouraging results, there are no prospective trials or retrospective large series with long-term follow-up supporting any evidences in favor of SABR versus surgery.

Therefore, also in the management of germ cell tumors metastasizing to the lungs, SABR should be alternative to

surgery when lung resection is not feasible. SABR should also follows the same selection criteria adopted for surgery.

Prostate cancer

Prostate cancer is the most frequent male malignancy in Europe with an incidence of about 200 cases every 1,000 men (41). Primary and secondary preventions have significantly improved prognosis and decreased metastases incidence. However, 6.7/100,000 cases have advanced disease at diagnosis (42). Otherwise, metastases could present later as metachronous recurrences despite controlled primary disease (43,44).

Metastases usually involve bone, bone marrow and regional nodes; visceral involvement is rare, about 15% of metastatic patients present lesions in liver, lungs, pleura, kidney and brain. Surprisingly, lung metastases are more frequent in autopsy than in advanced cases (25% versus 5.7%) (45). Unfortunately, visceral metastases are related to poor overall and disease-specific survival (42) compared to nodal and skeletal metastases (16 and 26 versus 43 and 61, 24 and 32 months respectively). Moreover, visceral metastases are rarely solitary (0.3%), since often present with contemporary bone or nodal involvement (46).

As in GCTs, oligo-metastases or oligo-recurrences are probably an intermediate state of disease progression, strictly correlated with the development and dissemination of other future distant metastases. Saitoh (46) has reported this theory in a paper that proposed two models in which (I) every metastasis originates from primary tumor or (II) metastases originate from other metastases. According to the second theory, their removal could stop the natural disease progression to very advanced and disseminate stage.

Surgery

At present, the gold standard of care for metastatic prostate cancer is hormonal deprivation by surgical or chemical castration, also named systemic androgen deprivation therapy (ADT) (47,48). Unfortunately, ADT is not curative but palliative and is generally continued until progression of the disease determining a cumulative toxicity over the years. Moreover, systemic therapy is often affected by many severe side effects such as sexual deficiency, bone fractures, anemia, vasomotor effects and cardiovascular injury.

Oligo-metastatic patients with visceral metastases could have different biological behavior and better prognosis

compared to other metastatic subgroups. Therefore, in selected cases, surgical metastasectomy might result in long-term survival and avoid ADT with its side effects. Main criteria for prostate cancer PM are consistent with general metastasectomy. They include control of the primary cancer, R0 achievement, no extra thoracic disease and cardiopulmonary function suitable for surgery. Consequently, preoperative staging became determinant to confirm that criteria have been met. Technetium-99 bone scan and whole-body CT scan have been used until the advent of choline PET scan. Correct staging combined with meticulous follow up, allows to effectively identifying this subgroup of patients (49,50).

Concerning optimal surgical approach, there are no evidences specific for prostate pulmonary metastases and criteria reported above for general and GCTs metastasectomy are reasonably applicable as well.

Literature about surgical treatment for pulmonary oligo-metastases in prostate cancer is poor and limited to case reports. Yao *et al.* (51), in their 2014 review, were able to find 4 cases of solitary prostate metastases treated by PM (52-55). Wallis *et al.* (56) have also cited these cases in a paper presenting also their single patient experience. They also cited some cases of multiple lung metastases without extra thoracic disease. These cases consisted of multi nodular, interstitial, endobronchial or pleural disease. Among them, just 3 cases obtained advantages by a combination of systemic and surgical therapy.

We have found two other recent cases of single pulmonary nodule surgically treated and resulting in postoperative undetectable PSA. The first one described by Rush *et al.* (57) in 2017 and the second by Mortier *et al.* in 2016 (58).

All the other cases reported in literature, despite oligo-metastatic state and PM, resulted in partial or absence of success as confirmed by increasing PSA and short survival (59,60).

It is common opinion that postoperative PSA decreasing to undetectable level is the prognostic factor for prolonged survival. Otherwise, it is logical to think that other sites of disease have been left undetected.

Reasonably, the few successful cases were those true oligo-metastatic and that is why surgery was able to alter natural history of the disease. Whereas, cases with undetected disseminated disease develop new metastases shortly after diagnosis. Unfortunately, according to many authors, incidence of recurrence after PM is high and ranges between 21% to 44.8% (61-63). However, the authors themselves do not discourage a re-operation. In fact, potential benefit arising from surgery in solitary pulmonary

nodule or oligo-metastatic cases is potentially curative and moreover avoid or delay side effects of ADT.

Non-surgical management

SABR

Local treatment, as an alternative to surgery, is represented by targeted radiotherapy. It can be delivered by conventional EBRT or by SABR. They act differently and SABR is supposed to induce an immune response favoring better tumor control.

The most common sites of metastasis treated by SABR are bone and regional nodes, in accordance with metastatic pattern frequency. Therefore, the most of series reported in literature does not address pulmonary metastases management.

Solitary lung oligo recurrences treated by radiotherapy are currently anecdotal in literature. At present, guidelines such as those from the National Comprehensive Cancer Network (NCCN) do not recommend ablative radiotherapy for curative metastatic prostate cancer therapy and define radiotherapy just a palliation for symptomatic patients.

Target therapy

ADT is the gold standard systemic therapy for hormonally sensitive prostate cancer (HSPC), whereas chemotherapy is adopted only in castration resistant patients (CRPC). However, in the last decade's introduction of new generation therapies has improved QoL and even survival.

ADT may determine changes in prostate tumor cells, leading to castration resistance. Many recent trials have shown that combination with new generation therapies could delay resistance's onset and improve survival. These therapies target the metabolic tumor pathways and act on changes induced by ADT itself. The efficacy of new generation hormones, abiraterone and enzalutamide, has been showed by many prospective randomized trials, both in pre and post chemotherapy setting (64,65). The AFFIRM trial (66), focused on the efficacy of enzalutamide post docetaxel, was able to show a progression free survival of 8.3 months against 5.4 months of placebo, at imaging founding. The COU-AA-301 (67) tested the efficacy of abiraterone in the same above conditions and found a progression free survival of 5.6 months (2.0 in placebo). Even higher rates of progression free survival (16.5 months) have been reported in PREVAIL trial (68,69) that showed how enzalutamide successfully reduces the risk of radiographic progression, improves survival and delayed chemotherapy.

Conclusions

At present, PM in Germ Cell Tumors and Prostate Cancer must be discussed in a multidisciplinary tumor board to provide a maximally “tailor-made” approach with an integrated approach consisting of systemic therapy or less invasive technique, such as term ablation or stereotactic radiotherapy.

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