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Case Report

Abscopal Effect in Radiotherapy Treatment

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Abstract

The abscopal effect is a phenomenon that occurs during the treatment of a metastatic cancer when the localized treatment of the tumor causes not only a shrinkage of the aforementioned, but also a shrinkage of tumors outside the scope of the localized treatment plan .The RT treatment also induced healing of metastases distant from the radiotherapy treatment plan, causing the abscopal effect even in lung and bone lesions with new diagnostic findings, confirming how Immunotherapy before and during the RT treatment makes the abscopal radiobiological effect not always predictable.

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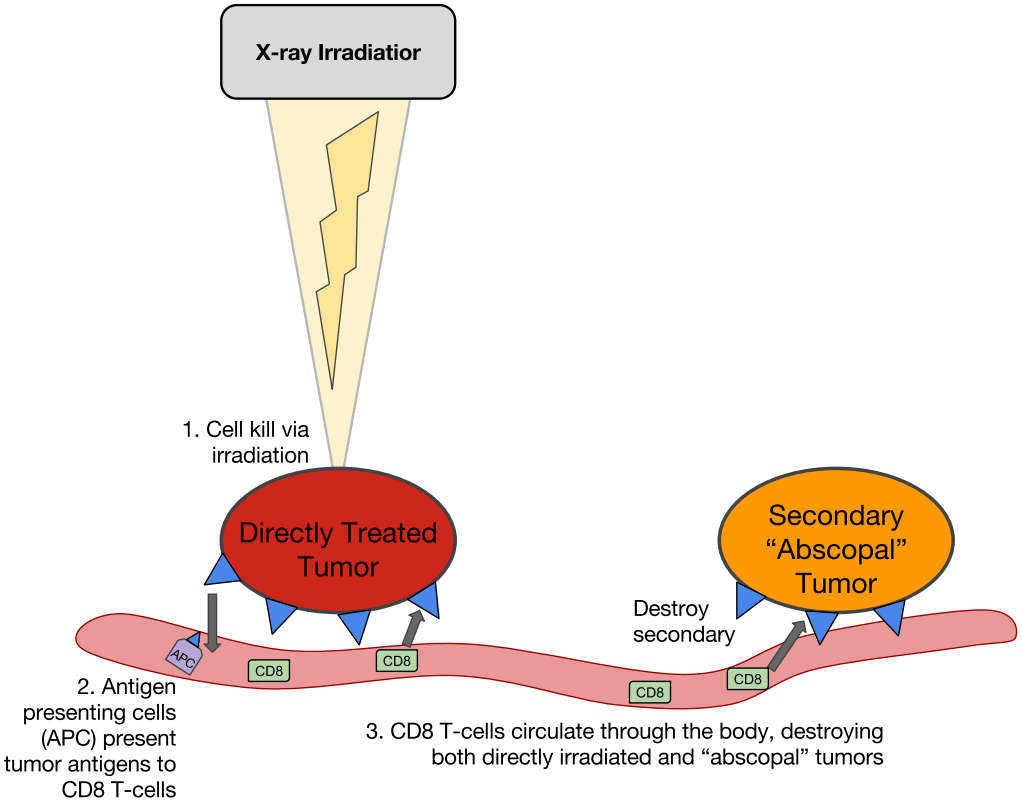
INTRODUCTION

The abscopal effect is a phenomenon that occurs during the treatment of a metastatic cancer when the localized treatment of the tumor causes not only a shrinkage of the aforementioned, but also a shrinkage of tumors outside the scope of the localized treatment plan. Richard H. Mole proposed the term abscopal (from the Latin ab, "far from", and scopus, "objective" in 1953 to refer to the effects of radiation "at a distance from the irradiated volume but within the same organism. Initially the Localized radiation therapy was associated with single tumor, but the phenomenon also includes other types of localized treatments such as electroporation and intra-tumoral injection of therapeutics is quite rare, but its effect on cancer can be astonishing leading to the possible disappearance of tumors. Such success has been described for a variety of tumors, including melanoma, lung cancer, cutaneous lymphomas, Hodgkin's and kidney cancer.



Despite the fact that in recent years there has been an increasing use of radiotherapy treatments hypo fractionated ablatives at high doses per fraction (stereotactic radiotherapy -SRT- and radiosurgery -SRS-), the radiobiological mechanisms that determine its effect are not yet completely clear. In fact, while some authors believe that the classical principles of radiobiology (4R: reoxygenation, repair, repopulation and redistribution), normally applied to conventional fractionations are sufficient to explain the excellent clinical results of hypo fractionated ablative radiotherapy, others argue that their role is limited. Recent In fact, preclinical data highlight that hypo fractionated ablative treatments cause death cellular or by a direct mechanism or, indirectly, through the alteration of the microenvironment. Other data have also demonstrated that the massive release of antigens from tumor cells killed directly or indirectly by high-dose radiotherapy stimulates anti-tumor immunity, reducing the risk of recurrence and metastasis. A more accurate understanding of the radiobiological mechanisms of response to radiation treatment high doses is of fundamental importance to more accurately predict short and long-term effects term both on the tumor and on the surrounding healthy tissues and consequently, improve the index therapeutic.

The 4 Rs of radiobiology

The 4Rs of radiobiology have a controversial role when schemes are employed hypo fractionated, especially if with high doses per fraction. In single fraction ablative treatments, reoxygenation cannot influence the response tumor, given the massive vascular destruction in tumors after high-dose irradiation. However, the drastic reduction in oxygen consumption by dying tumor cells massive could favor the reoxygenation of surviving hypoxic cells. Furthermore, you can have a certain amount of reoxygenation when using doses of 3-8 Gy per fraction given that in these cases the vascular damage may be irrelevant. Irradiation with high doses per fraction, requiring a prolonged delivery time, can interfere in the repair mechanisms of sub-lethal damage. In fact, a loss was demonstrated of approximately 10% of the biological effectiveness when the duration of treatment delivery was more than thirty minutes. Furthermore, it can be assumed that irradiation at high doses per fraction you create a saturation of the repair mechanisms due to exhaustion from consumption of the enzymatic pool. Hypofractionations with high single dose values can interfere with redistribution, blocking the cell in the cell cycle phase it was in at the time of irradiation and however, it is possible that some cells may slowly progress to G2 and then undergo a death. In hypo fractionated ablative treatments, repopulation is not considerable. Indeed, Typically, this occurs due to the proliferation of cells that are not killed by radiation ionizing 3-4 weeks after the start of radiotherapy, while SRT ends in a long time shorter. However, it is possible that a certain degree of repopulation evoked by the depletion of the cell population and that this occurs earlier than conventional treatments.

The Quadratic Linear Model

The quadratic linear model, through mathematical formulas (BED, EQD2) is used to calculate is effective doses for fractionations other than conventional. Based on intake that radio-induced cell death is mainly due to breaks in the DNA double helix, is considered valid for fractions from 1 to 5 Gy, while its usefulness is probably limited when they use higher doses per fraction. The LQ model derives from studies carried out mainly in vitro and does not perfectly reflect what is observed in vivo. Based on observations carried out in vitro, it is believed on the one hand that the LQ model can overestimate cell death resulting from high doses per fraction because the survival curve increases as the dose increases cellular depends on the quadratic component of the formula, while at high doses for single fraction, the linear component of the damage prevails. The LQ model also does not allow you to consider the vascular component of the damage which is observed in vivo mainly at high doses for a single fraction. Finally, another limitation of the LQ model is that it does not take existence into account of tumor stem cells, responsible for maintaining the tumor pool and characterized by greater radio resistance than normal tumor cells. Despite these data, it was demonstrated in experimental models and observed in some clinical situations that the LQ model does adequately suited to the response to SRT treatments with high single dose values and which can be reliable for single fraction doses up to 10 Gy, becoming progressively less accurate above these doses. Therefore, it is possible that in certain situations cell death is calculated with the LQ formula cannot overestimate, but approximate the total cell death caused by SRT. This can happen when cell death is not mediated only by a direct action on the cell's cells, but also by a marked indirect component. Although the linear-quadratic model is the most commonly used, other models, such as Universal Survival Curve (USC), were introduced to compare conventional schemes with hypo fractionated ones employing high doses per fraction, providing both an empirical rationale that clinical for SRT.

The Main Radiobiological Target of High-Dose Radiotherapy: Tumor Cells or Cells Endothelial?

The radiobiological target underlying the response to high-dose radiation treatments is a topic of heated debate. By applying the principles of classical radiobiology, according to which the main target of the radio-induced damage is the DNA and cell death is essentially due to the breakdown of the double helix, we should expect a smaller biological effect than what is observed experimentally and clinically. Indeed, although Leith *et al*. have calculated, according to the principles classics of radiobiology and taking into account the presence of hypoxic cells, which to control a brain tumor of 3 cm in diameter would require doses of at least 80-90 Gy in fractions single fraction (2-7,11,20,21), many clinical studies have demonstrated that 18-25 Gy in a single fraction is highly effective in controlling primary and metastatic central nervous system tumors). Another example, in 5-7 cm liver tumors treated with 54 Gy in 3 fractions, local control was greater than 90% for 2 years (24). To justify these surprisingly better clinical results than expected by applying principles of classical radiobiology (as carried out in the study by Leith *et al.*, were proposed radiobiological mechanisms other than direct cell death by double rupture DNA strand. The most accredited hypothesis holds that radiation administered at high doses causes damage to endothelial cells resulting in deterioration of the tumor microenvironment and indirect cell death due to hypoxia. It has been demonstrated that tumor endothelial cells are more radiosensitive than normal endothelial cells due to both a different intrinsic radiosensitivity and structural differences. There is various experimental evidence to support the theory of damage to endothelial cells. It has been demonstrated that doses higher than 10 Gy in a single fraction cause vascular damage of various types (occlusion, vasodilation, vasoconstriction, rupture) associated with a decrease in the number of endotheliocytes with consequent reduction in perfusion. In support of the indirect role of vascular damage, in mice irradiated with 10 Gy in a single dose was observed lower clonogenic survival when tumors were left in place compared until they are transferred in vitro. The dose needed to cause indirect death may vary based on various factors such as tumor type and vessel diameter. Indeed, small vessels diameter vessels appear to be more vulnerable to radiation damage than diameter vessels greater. Despite these data, there is consensus on what the main target of damage in treatments is hypo fractionated at high doses is not unanimous. In a recent study in the mouse model, Moding *et al*. argue that this is represented by the tumor cell rather than the endothelial cell. This hypothesis is supported by the demonstration that radiation-induced tumor death does not vary when Endothelial cells are genetically modified with deletion of the pro-apoptotic gene Bax or del DNA damage response gene ATM. While not excluding a possible role of other cells stromal in the eradication of the tumor with SRT, the authors reduce the contribution of the damage vascular.

Damage From Antigen Release and Role of The Immune Response

There are other biological mechanisms involved in the effectiveness of high-dose ablative treatments. AND' High-dose hypo fractionated irradiation has been reported to promote antitumor immunity, while fractionated treatments with low doses per fraction suppress immunocompetence of the guest. Extensive cell death during hypo fractionated irradiation induces an increase in expression of immunomodulatory molecules such as the histocompatibility complex, molecules of adhesion, heat shock proteins, inflammatory mediators, immunomodulatory cytokines death receptors on the surface of tumor cells. The massive release of tumor antigens and cytokines determines an increase in the innate anti-tumor response. In a mouse model in which a B16 melanoma had been induced, irradiation with 15 Gy in a single dose determined an increase in the number of anti-tumor immune cells facilitating the presentation of antigens, the priming of T lymphocytes in lymph nodes and the trafficking of effector T lymphocytes into tumors. When the same dose was fractionated in the same mouse model, the immune response was inferior, while increasing the single dose up to 20 Gy increased the response immune to the primary tumor. The role of anti-

tumor immunity has been observed also in clinical studies. In a recent phase 1 study it was demonstrated that the association of IL-2 with SRT is able to enhance the immune response compared to radiotherapy alone. The association of ipilimumab, a CTLA-4 ligand, with SRT (9.5 Gy in 3 fractions) has determined the onset of the abscopal effect in metastatic melanoma. It's important emphasize that the complete development of tumor-specific radiation-induced immunity occurs generally in 1-2 weeks and therefore cannot be responsible for the secondary death of tumor cells that is observed 2-3 days after radiation treatment. Radio-induced tumor-specific immunity appears to be able to inhibit the proliferation of surviving tumor cells, thus leading to the suppression of relapses and metastases.

Case Report

The patient dates the onset of his current clinical condition to January 2024 when pain in the lumbar region radiated to the abdominal level, on 02/15/2024 he performed a complete abdomen ultrasound: in the liver hypodense nodular formations in the VI segment with a dtm of 16mm in the fourth segment with a dtm of 31mm in the sixth segment with a dtm of 15mm. The findings described are not evident upon previous examination instrumental performed on 01/30/23 performed at another location. Diagnostic interrogation is required with imaging and level II CT abdomen with contrast medium. Prostatic glandular parenchyma altered by the presence of a nucleus of subcervical adenomatosis with intravesical manifestation of the third lobe. 02/20/2024 performed CT abdomen and thorax with contrast medium:

CHEST: solid nucleus with irregular spiculated margins on the paramediastinal side of the right lung parenchyma, with transcissural development between the LM and the lower lobe (max dm 46x28mm). Lesion is inseparable from the parietal pleural plane in contiguity of the right atrial chamber. Multiple nodular thickenings of the right major and minor fissures (DM 7.5mm) and of the pleural planes, in particular on the mediastinal side of the LSD (DM 12mm) and on the parietal plane costal and diaphragmatic of the LID (DM 8.5mm). Pathological lymphadenopathy at the right paratracheal level (DM 22x21mm), right hilar (DM 24x21mm) and in the context of the right pulmonary ligament (DM 18x16mm). Peri lymphatic micronodules in the LID (DM 4mm) and in the Middle Lobe (DM...). Suspicious findings for trial pathological of pulmonary origin with lymph node and pleural localizations. Millimetric nodularities in the moles lingular segments (DM 4.5mm) and at the level of the basal segments of the LIS (DM 5mm). Thin pericardial layer.

ABDOMEN: liver with hypovascular oval formations in the liver parenchyma of pathological significance secondary, the largest in segments V (DM 23mm), VII (DM 13mm) and VIII (DM 8mm). Solid nodule in left lateral adrenal arm (DM 27mm). Minor nodules in the right adrenal parenchyma (DM 10mm). Suspicious findings due to secondary localizations. Moderately increased volume prostate DT 51mm ca SKELETON: extensive osteolytic alteration of the D8 vertebral body, on the left side (DM 20mm). Similar skeletal alterations of the vertebral somata D2 (DM 5mm) and D3 (DM 10mm) with depression of the upper somatic limit. 03/04/2024 the patient underwent "Videomediastinoscopy - biopsies" surgery lymph nodes"

EI Exam n°: I/ 2024/ 2370 of 03/04/2024 Repetitive lymph node localization of adenocarcinoma, with acinar growth pattern with immunophenotypic structure (CK7+, TTF1+, NapsinA+) consistent, also in light of the clinical-radiological picture, with pulmonary primitiveness. PDL1 10-15% .

03/16/2024

Oncology video, evaluation will be scheduled for indication of medical therapy with Denosumab. NGS DNA/RNA required.

03/28/2024

I VISIT, 57-year-old patient suffering from stage IV lung cancer (bone, liver, adrenals), underwent on 04/03/2024 to "Videomediastinoscopy - lymph node biopsies" surgery EI Exam n°: I/2024/ 2370 of 04/03/2024 Repetitive lymph node localization of adenocarcinoma, with pattern of acinar growth with consistent immunophenotypic structure (CK7+, TTF1+, NapsinA+), even in light of the clinical-radiological picture, with pulmonary primitiveness. PDL-1 10-15%.

03/16/2024

Oncology Video: evaluation will be scheduled for indication of medical therapy with Denosumab. NGS DNA/RNA required. Neurosurgical video to be evaluated for possible positioning of a support bust/other intervention. RT treatment is indicated on D8 in 10 fractions. Prescribed bust C35.

02/04/2024

Lung PDTA Discussion Today: indication for PET/CT and MRI of the spine with contrast medium and subsequent neurosurgical evaluation.

MRI of the Cervical Spine Without and With Contrast, MRI of The Dorsal Column Without and With Contrast, MRI Lumbosacral Spine Without and with MDC

Test performed using equipment operating at 1.5T with acquisition of suitable sequences to the evaluation of the region of interest. Having read the previous PET-CT investigation performed here on 04.04.2024. Today's examination confirms the presence of multiple secondary lesions, characterized by 04/15/2024 hypersignal in STIR enhancement after contrast medium, widespread almost ubiquitously in the context of bone spongiosa of the metamers examined; in particular, the largest lesion is located at the level of the soma of D8 where the swollen appearance of the posterior wall is appreciated, with extension of the pathological tissue in the context of the vertebral canal (in the absence of intramedullary alterations) and at the level of the lateral paravertebral space a left with involvement of the ipsilateral cost-vertebral joint. Absence of structural failures of the vertebral bodies examined. Alterations of similar significance are also appreciated at the level of the sacrum, of the iliac wings, at the level of the left ilium, and at the level of the

neck and the left femoral shaft. Signal alteration is documented in the context of the spinal cord at the metameric level D9, Anterolateral side on the right, characterized by marked hypo signal in T2 sequences, to be reported probably a small cavernoma. Neurosurgical evaluation performed) which currently does not indicate an indication for surgery of vertebral stabilization D8 due to the presence of disease on the adjacent vertebrae. Palliative radiotherapy is indicated.

04/04/24
PET/CT TOTAL BODY FDG
The tomoscintigraphic examination documented:
- **In the Pulmonary Field:** pathological fixation of the radiopharmaceutical (SUVmax 12.04) on the load of the radiologically known tissue thickening detectable in the right paramediastinal lung area, with development transcissural between LM and LID, and difficult to dissociate from multiple metabolically active lymphadenopathies in the ipsilateral hilar site; downstream of this lesion, again in the medial segment of the LM, an altitude of atelectatic lung parenchyma faintly FDG uptake; they are also reported in the lungs bilateral multiple FDG-enhancing nodulations at the LSD in the paramediastinal and anterior subpleural areas, at the LID in the basal segments and in the posterior/posterolateral subpleural areas, as well as at the LSS in the anterior subpleural areas;
- **In the lymph Node Area:** pathological uptake of FDG due to combined lymphadenopathy in the right lower paratracheal, subcarinal and right hilar-pulmonary areas (already mentioned above), as well as due to lymph node swelling in the right retrocrural area;
- **In The Liver:** areas of pathological fixation of the radiopharmaceutical of a focal nature affecting the VII/VIII hepatic segment (at least two), to the IVa segment, to the VI segment and to the IVb segment at the most extensive and capturing showing necrotic central core (SUVmax 14.4);
- **In the Splenic Site:** focal radioconcentration (SUVmax 7.2) near the pole.

04/15/2024
Inferior;
- **In the Bilateral Adrenal Area:** pathological FDG uptake (SUVmax on the left 14.9);
- **In the Bone:** multiple predominantly lytic and metabolically active lesions affecting the diaphysis left humeral bone, proximal end of the right clavicle, sternum in multiple locations, left scapula, arch anterior of the left VIII rib, posterior arch of the VI and IX right rib, right hemiarch of C1, C3, C6, multiple dorsal vertebrae (among which we note the one on D8 with an osteodestructive character leading to lysis of the posterior wall), to loading of L3, L4, L5, sacrum in multiple locations, right iliac wing, posterior articular aspect, wing and acetabulum of the ilium of left, left ischial tuberosity, left femoral neck;
- **affecting soft tissues:** multiple focal radio concentration spots, the most relevant affecting the m. left deltoid, affecting the periarticular tissues of the right scapulohumeral joint, in the context of the m. great left gluteus and m. right gluteus medius, m. sartorio on the right and on the m. left vastus lateralis.

Conclusions: Presence of disease with high glucose metabolism in the locations described.

04/16/2024
Performs CTG: Patient in fair general clinical condition, denies new noteworthy disorders. Internal images.

04/19/2024
Performs cervical spine CTG: Patient in good clinical condition. He denies new onset disorders.

04/22/2024
START RT 1/10 on dorsal column
Patient in good general clinical condition, denies new noteworthy disorders.

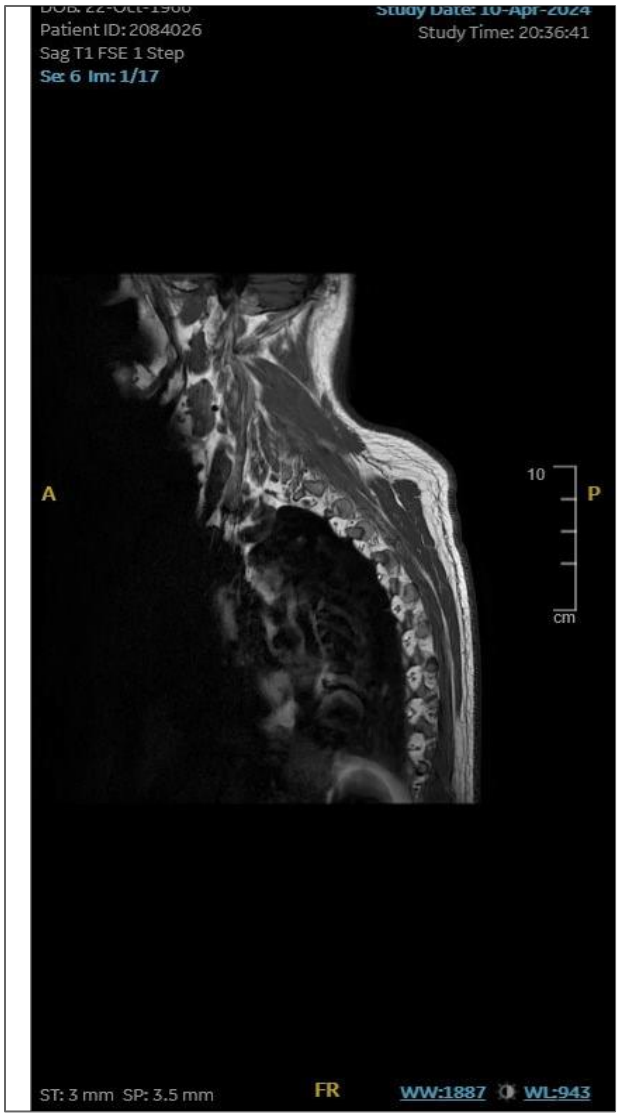
Denies pain in vision: EE dated 6.3.24 GR 4.1 HB 11.8 GB 7.19 PLT 309
Refalgin sachets x2/day are prescribed.
EE of 12.04.24 GR 5.08 HB 13.9 GB 9.23 neu 3.7 lymph 4.2 PLT 358 hepatic fx normal 04.24.2024 EE: rbc: 5.34, hgb: 14.6, wbc: 9.68, neu: 4.95, lin: 4.07, plt: 312, renal function ed liver normal.

04/30/2024
CONTINUED RT 4/10 D7-D9, 2/10 C2
Patient in good general clinical condition, denies new noteworthy disorders. Denies pain EE sent by email.

05/07/2024
CONTINUED RT 8/10 D7-D9, 6/10 C2
Patient in good general clinical condition, denies new noteworthy disorders. Denies pain.

Sent via email:
08.05.2024 EE:rbc: 5.3, hgb: 15.2, wbc: 5.77, plt: 217creatinine: 0.9, eGFR: 87, AST: 42, ALT: 46, bilirubin TOT: 0.5, DIR: 0.2

05/13/2024
ENDS RT 10/10
Patient in good clinical condition. Denies new onset disorders.
On therapy with Brigatinib 180 mg/day. The treatment was well tolerated and did not undergo interruptions. The patient is referred to the attention of oncology colleagues for the continuation of the therapeutic process.



MRI OF THE CERVICAL SPINE WITHOUT AND WITH CONTRAST, MRI OF THE DORSAL COLUMN WITHOUT AND WITH CONTRAST, MRI OF THE LUMBOSACRAL SPINE WITHOUT AND WITH CONTRAST

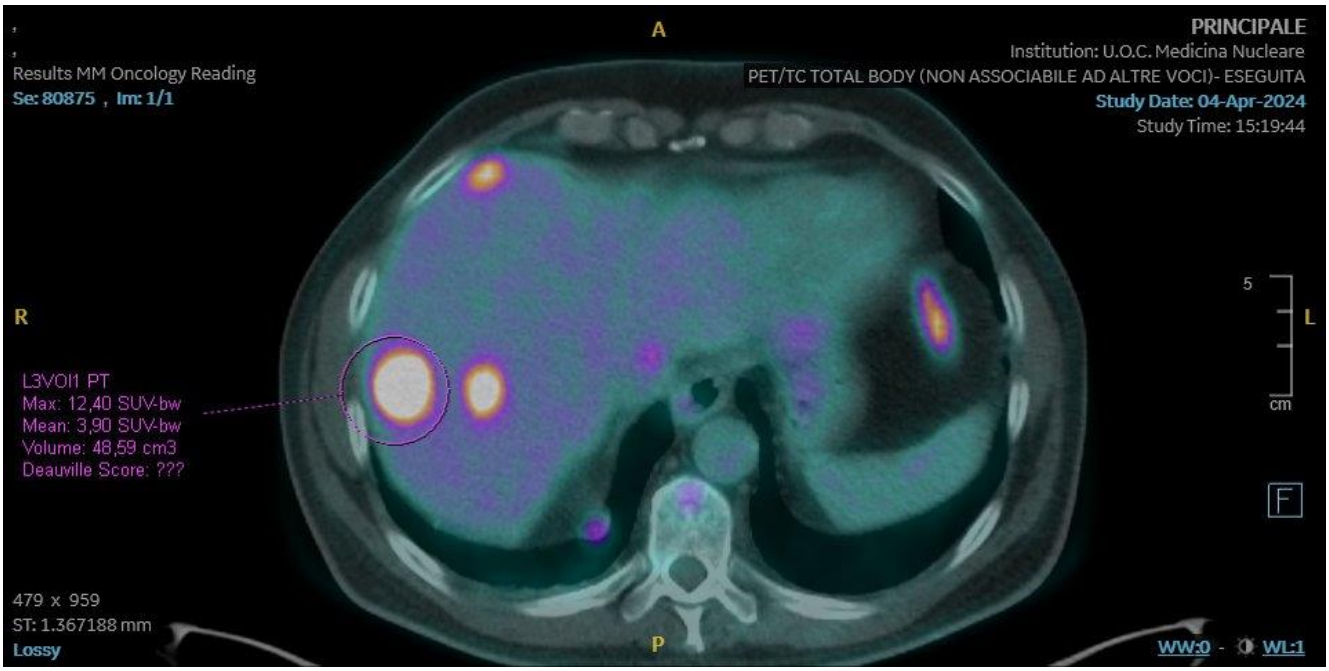
Examination performed using equipment operating at 1.5T with acquisition of sequences suitable for evaluating the region of interest. Having read the previous PET-CT investigation performed here on 04.04.2024. Today's examination confirms the presence of multiple secondary lesions, characterized by hypersignal in STIR and enhancement after contrast medium, spread almost ubiquitously in the context of the bone spongiosa of the metamers examined; in particular, the largest lesion is located at the level of the soma of D8 where the swollen appearance of the posterior wall is appreciated, with extension of the pathological tissue in the context of the vertebral canal (in the absence of intramedullary alterations) and at the level of the lateral paravertebral space on the left with involvement of the ipsilateral cost-vertebral joint. Absence of structural failures of the vertebral bodies examined. Alterations of similar significance are also appreciated at the level of the sacrum, of the iliac wings, at the level of the left ilium, and at the level of the neck and the left femoral diaphysis. Signal alteration is documented in the context of the spinal cord at the D9 metameric level, on the anterolateral side on the right, characterized by marked hyposignal in the T2* sequences, probably referring to a small cavernoma.

PET/CT TOTAL BODY (NOT ASSOCIATED WITH OTHER ITEMS) - PERFORMED WITH A HYBRID PET/CT MACHINE, NUCLEAR MEDICAL CHECK-UP EXAMINATION

The preliminary evaluation of the patient determines a judgment of suitability for carrying out the test, considered irreplaceable for obtaining the diagnostic information required by the clinical question. N.B. Also valid as a declaration of radiopharmaceutical administration in compliance with current regulations.

Clinical indication: staging in patients with recent diagnosis of lung adenocarcinoma. CT scan dated 02.20.24 performed at Another Center documents "THORAX: solid nucleus with spiculated margins on the right paramediastinal side of the lung, lesion indissociable from the parietal pleural plane with contiguity of the right atrial chamber, multiple nodular thickenings in particular on the mediastinal side of the LSD and on the parieto-costal and diaphragmatic of the LID... pathological lymphadenopathies at the right paratracheal, right hilar and in the context of the right pulmonary ligament, peri-lymphatic micronodules in the LID and in the LM. ABDOMEN: liver lesions of secondary significance, the largest in the V segments, VII and VIII, solid nodule in the left adrenal gland, minor nodules in the right adrenal gland: suspicious findings for secondary localizations of the disease. SKELETON: extensive osteolytic alteration of the vertebral soma of D8, on the left side, similar alterations of the vertebral soma of D2 and D3".

On 04.03.24 Videomediastinoscopy with lymph node biopsies with E.I. was carried out. "Repetitive lymph node localization of adenok with acinar growth pattern (CK7+, TTF1+, NapsinA+) consistent with pulmonary primitiveness".
Blood sugar before administration: 110 mg/dl.
Technique: The examination was performed on an empty stomach, with PET technique, after intravenous administration of 18F-FDG and with 3D mode. Images of the distribution of the radiopharmaceutical were acquired from the orbito-meatal line to the middle third of the femur. Multi-planar tomographic sections corrected for photonic attenuation were reconstructed using a low-dose CT method. The brain parenchyma cannot be evaluated due to the intrinsic limitations of the method, so please refer to dedicated studies (brain MRI/CT).



Report:
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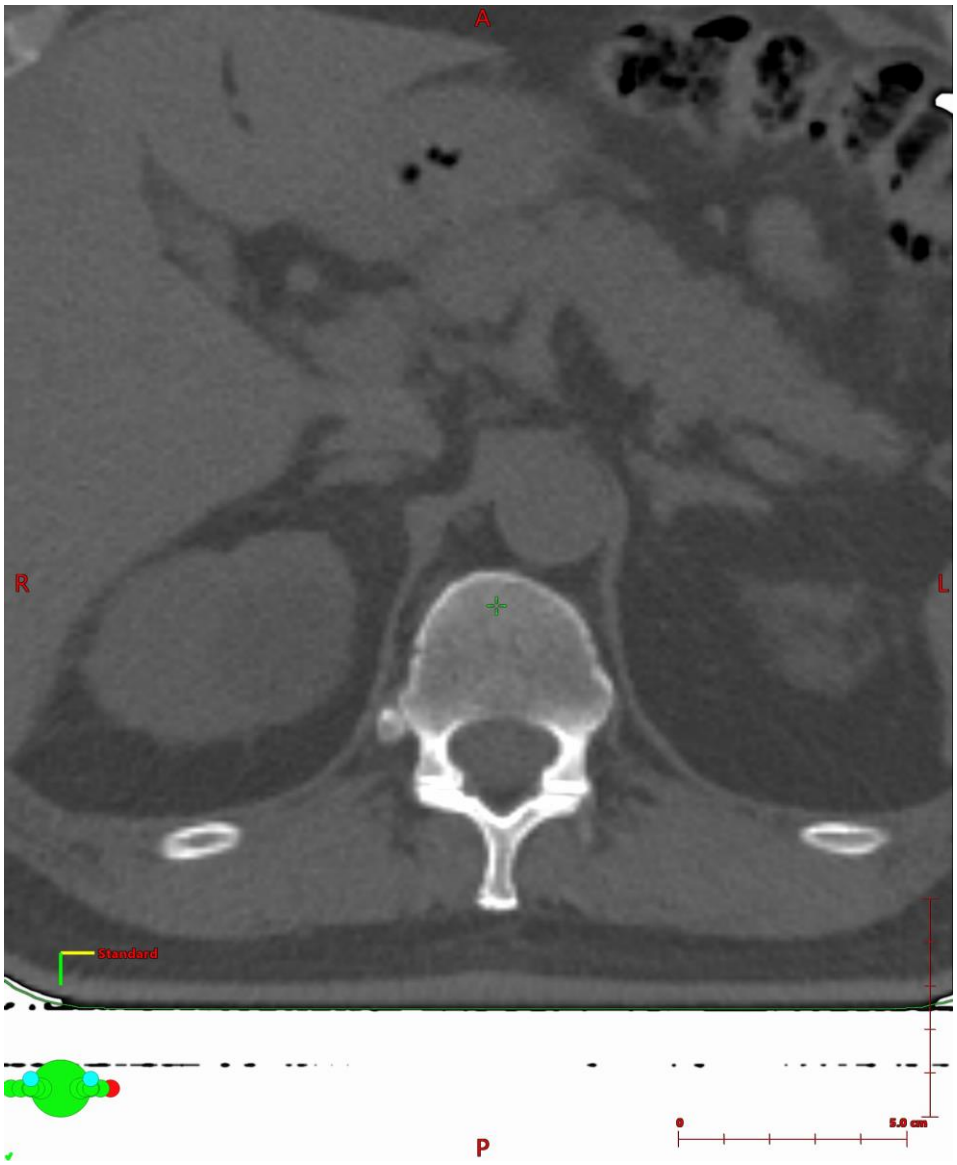
- **In The Splenic Site:** focal radioconcentration (SUVmax 7.2) near the lower pole;
- **In The Bilateral Adrenal Area:** pathological FDG uptake (SUVmax on the left 14.9);
- **In The Bone:** multiple predominantly lytic and metabolically active lesions affecting the left humeral diaphysis, proximal end

of the right clavicle, sternum in multiple locations, left scapula, anterior arch of the left VIII rib, posterior arch of the VI and IX right rib , right hemiarch of C1, C3, C6, multiple dorsal vertebrae (among which we note the one on D8 with an Osteodestructive character resulting in lysis of the posterior wall), affecting L3, L4, L5, sacrum in multiple locations, right iliac wing, side posterior articular, wing and acetabulum of the left ilium, left ischial tuberosity, left femoral neck;

- affecting soft tissues: multiple focal radioconcentration spots, the most relevant affecting the m. left deltoid, affecting the periarticular tissues of the right scapulohumeral art, in the context of the m. left gluteus maximus and m. right gluteus medius, m. sartorio on the right and on the m. left vastus lateralis.



PLAN RT DOSES AND TREATMENT PLAN

Conclusions: Presence of disease with high glucose metabolism in the locations described. Concludes RT 10/10 Patient in good clinical condition. He denies new onset disorders. On tp with Brigatinib 180 mg/day. The treatment was well tolerated and did not undergo interruptions. The patient is referred to the attention of oncology colleagues for the continuation of the therapeutic process.

CONCLUSIONS

The RT treatment also induced healing of metastases distant from the radiotherapy treatment plan, causing the abscopal effect even in lung and bone lesions with new diagnostic findings, confirming how Immunotherapy before and during the RT treatment makes the abscopal radiobiological effect not always predictable.

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