



Anaplastic thyroid carcinoma: Rare clinical case of extrathyroidal primary retroperitoneal tumour and review of literature

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Abstract

Anaplastic thyroid carcinoma is a very rare type of undifferentiated thyroid carcinoma. Mostly, the ATC is diagnosed in advanced stage when local and distant metastases are detected. Multimodal approach and personal treatment managed by a multidisciplinary team of specialist is recommended in all ATC cases. Despite new treatment methods this type of cancer has a very poor prognosis due to fast growth and invasiveness, airway problems and failures of distant metastases control. We present a very rare case of occurrence of anaplastic thyroid carcinoma in the extrathyroidal area. Primary fast growing retroperitoneal tumor with differentiation of anaplastic thyroid carcinoma was diagnosed to a 72-year-old female when no changes were detected in thyroid glands. Due to severe patient status, abdominal pain, and mass effect on surrounding organs caused by suspected retroperitoneal tumor urgent resection surgery was performed. Histopathology analysis confirmed diagnosis of primary retroperitoneal cancer with differentiation of anaplastic thyroid cancer. Later suspected metastases in the left subclavicular lymph node were found but the patient refused further investigation and treatment. Even though the patient is still alive more than 2 years after initial diagnosis and represents a better survival than is described in the literature.

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Introduction

Anaplastic Thyroid Carcinoma (ATC) is known as a highly aggressive type of cancer with a very poor prognosis [1,4]. ATC is a form of undifferentiated thyroid carcinoma and represents 1-2% of all thyroid tumours [2,5,6]. Despite being extremely rare, it accounts for up to 50% of all thyroid cancer-related mortalities [2,3]. The median survival rate varies, usually 3 to 6 months after the diagnosis [1,2,4,7,8]. The overall 1-year and 5-year

survival is 10-20% and less than 10% respectively [4,6,7]. ATC's origin is unknown. As a form of undifferentiated thyroid cancer it can arise de novo or from a pre-existing well-differentiated thyroid tumour due to the accumulation of genetic alterations [6,9,14]. ATC is exceptional because of its high aggressiveness, fast growth, and strong invasiveness [5,6]. This type of cancer often presents with metastases to local and distant lymph nodes, lungs, and liver [15,16]. ATC is more common in women and people over the age 60 [2,8,15,17,18]. Distant metastases,

age, and socioeconomic status are other known risk factors associated with poorer survival in these patients [15,19]. Various strategies of treatment are used for ATC such as surgical resection, radiation therapy, chemotherapy, immunotherapy, or a combination of different treatment methods [8,20]. Usually, the treatment of choice depends on the specific situation [20,21].

Little is known about extrathyroidal ATC. We represent a current knowledge about ATC in extrathyroidal area focusing on the primary retroperitoneal tumours. We also describe a very unique case of a patient with a huge primary retroperitoneal tumour of ATC origin with normal function and structure of thyroid gland.

Case report

A 72-year-old woman was admitted to our hospital due to a high fever of up to 42 degrees Celsius, acute abdominal pain, and loss of consciousness. Increasing abdominal growth and abdominal pain lasted for more than a week. Abdomen ultrasound showed a massive cystic-solid abdominal mass causing mass effect on surrounding organs.

Computed Tomography (CT) imaging was made for diagnostic clarification, huge. ~26x23x27.5 cm in homogeneous (cystic-solid mass with calcinates) abdominal mass. (likely to be an ovarian tumour) was detected causing left hydronephrosis (Figure 1) (Large intraabdominal well defined mass (large arrow) with periferal calcifications, predominant cystic component and solid contrast enhancing tissue (thin arrow) by the left wall, where a small arterial pseudoaneurysm (asterix) is seen), 2). Illness anamnesis, health, and family history were unknown at that time due to severe patient status. Later the patient explained that she noticed an increasing size of her abdomen over many years (around 30 years) but she did not consult with the doctors. During check-up in the emergency department patient was conscious but assessed as having SCORE 12 on Glasgow Coma Scale (GCS), hemodynamically unstable, hypotonic and having respiratory failure (hypoxia, acidosis). Increased inflammatory indicators (C-reactive protein 167 mg/l), procalcitonin (174 µg/l), D-dimers (31670 µg/L), lactate (>5 mmol/l), anaemia (haemoglobin 109 g/l) and coagulation indicators imbalance were detected. Due to large abdominal mass compression of the left ureter which caused left hydronephrosis urologist performed a left percutaneous nephrostomy. The patient underwent an urgent operation: extirpation of retroperitoneum tumour with left hemicolectomy and formation of an end colostomy. The abdominal cavity was occupied with pathological retroperitoneal mass in the mesentery of large intestines with a very close connection with descending and sigmoid colons and also invaded arteria mesenterica inferior (Figure 4). The post-operative course was smooth. After the operation conservative treatment was provided: antibiotic therapy, vasopressors, analgesics, infusion therapy, anticoagulation prevention, and other. In dynamics, the patient's condition improved, inflammatory and uremia indicators decreased, and left kidney nephrostomy was removed. The patient was discharged, and the whole duration of hospitalization was less than two weeks. During the late post-operative period the patient had no health complaints. At that time, results of histopathological analysis of the retroperitoneal tumour came out: thyroid papillary carcinoma with anaplastic carcinoma differentiation, invasion of anaplastic carcinoma to the large intestine. After a month the patient was consulted repeatedly. Blood tests (thyrotropin-releasing hormone, anti-thyroglobulin, thyroglobulin, a carcinoembryonic antigen) were done, and results were in a normal range. A thyroid ultrasound

was done, and only minor insignificant diffuse changes were seen in thyroid tissue and one supraclavicular pathological lymph node (7x15 mm) was detected on the left. Neck, chest, abdomen, and pelvic CT was performed two months after the operation, borderline left subclavicular lymph node (14x10 mm) was seen, and no focal metastases in the lungs and internal organs were detected. The future treatment plan was discussed by the multidisciplinary group of doctors (abdominal surgeon, oncologist-chemotherapist, radiologist, endocrinologist). The patient was suggested to undergo a positron emission tomography (PET) scan, and later have a biopsy taken from the borderline left subclavicular lymph node, no adjuvant treatment was suggested at that time. However, the patient refused further investigation and treatment. Overall, the patient survived more than 5 months after the operation, no adjuvant treatment was given. The patient did not have any complains, and no signs of disease recurrence or metastases were seen except for the borderline left subclavicular lymph node. In addition, the patient is still alive 2 years after the primary operation and initial diagnosis of primary retroperitoneal cancer with ATC differentiation. A detailed description of histopathological analysis was done. The resected retroperitoneal tumour is a thyroid papillary carcinoma with anaplastic carcinoma differentiation and invasion to the large intestine. The resected yellow-grey retroperitoneal mass measuring 30 cm in the greatest dimension with necrotic areas and haemorrhages in the centre. Extensive sampling showed various sizes of follicular, glandular and papillary structures, atypical in shape epithelium cells with eosinophilic cytoplasm and oval, round slightly polymorphic nuclei. Little mitosis was found. The malignant tumour was encapsulated. Less than 5% of the tumour was composed of large atypical epithelioid cells with eosinophilic cytoplasm, polymorphic, vesicular nuclei, and conspicuous nucleoli and high mitotic activity (anaplastic transformation). More clusters of atypical cells were found in fibrotic capsules with overgrowth (Figure 5-7 (High-grade tumour component, making up 5% of total tumour area, is composed of large epithelioid cells with eosinophilic cytoplasm, polymorphic nuclei with extensive necrosis, apoptotic and mitotic figures. Some tumour cells are large with multiple nuclei (Photomicrograph, HE stain))). Immunohistochemical staining was also performed. The tumour cells were strongly positive for Anti-Cytokeratin (Cam5.2), Pan-Cytokeratin (PanCK), Cytokeratin 19 (CK19), thyroglobulin, and Thyroid transcription factor-1 (TTF-1). Half of the cells showed positive results for PAX8 and Epithelial membrane antigen (EMA), and less than 5% of cells – protein Ki67. P53, BRAF, WT1, synaptophysin, estrogen receptors were negative (Figure 8). Histological analysis and the overall immunohistochemical profile were concluded to final diagnosis of a primary retroperitoneal tumour of thyroid papillary carcinoma with focal transformation to thyroid anaplastic carcinoma of high grade (G4) malignancy (anaplastic carcinoma giant cell carcinoma type).

Anaplastic carcinoma can be found in the retroperitoneal area due to several reasons: as primary thyroid cancer, as a struma ovarii with malignant transformation and metastases to the retroperitoneal area, or as a metastases of papillary cancer with anaplastic transformation when a primary tumor is found in the thyroid. According to the blood tests and imaging results, the patient in our case presented with primary retroperitoneal cancer with differentiation of ATC. Written informed consent from the patient for the publication of any possible identifiable information (images and case details) was obtained.

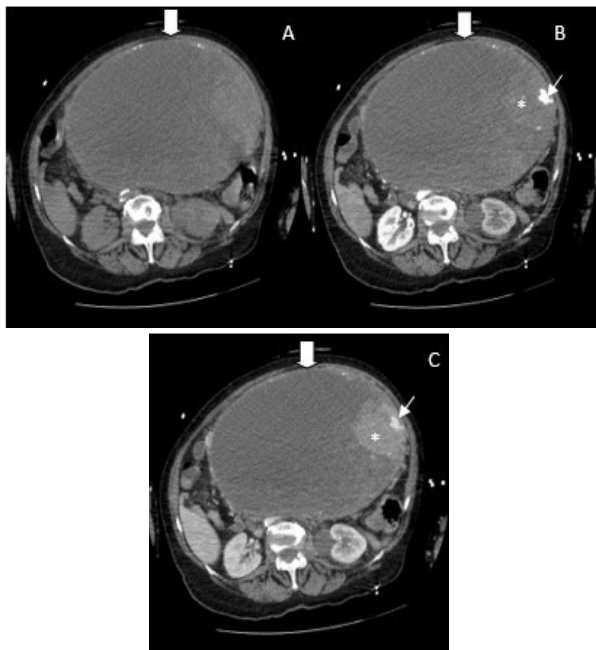


Figure 1: Abdominopelvic CT scan axial plane, non-contrast (A), arterial (B), portal (C) phases.



Figure 2: Before primary surgery. Huge abdomen and catheter of left percutaneous nephrostomy is seen.

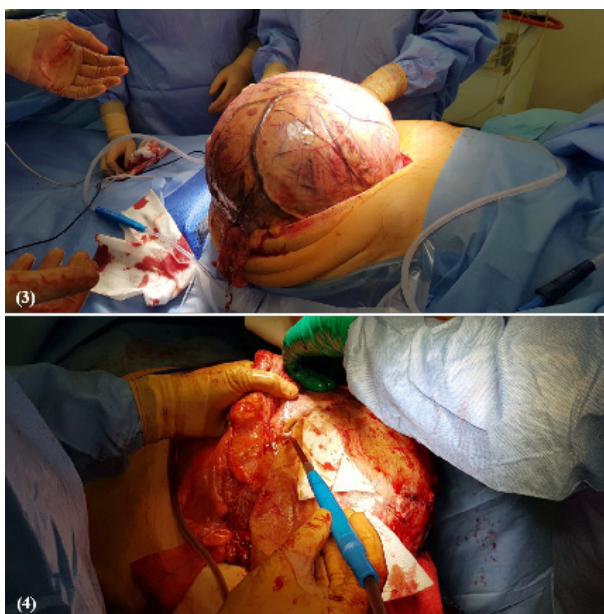


Figure 3 & 4: Abdominal cavity was occupied with huge pathological retroperitoneal mass.

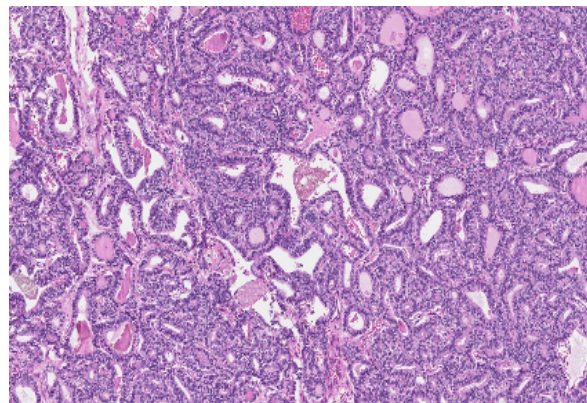


Figure 5: Well differentiated tumour component composed of papillary, glandular structures (filled with colloid (Photomicrograph, HE stain)).

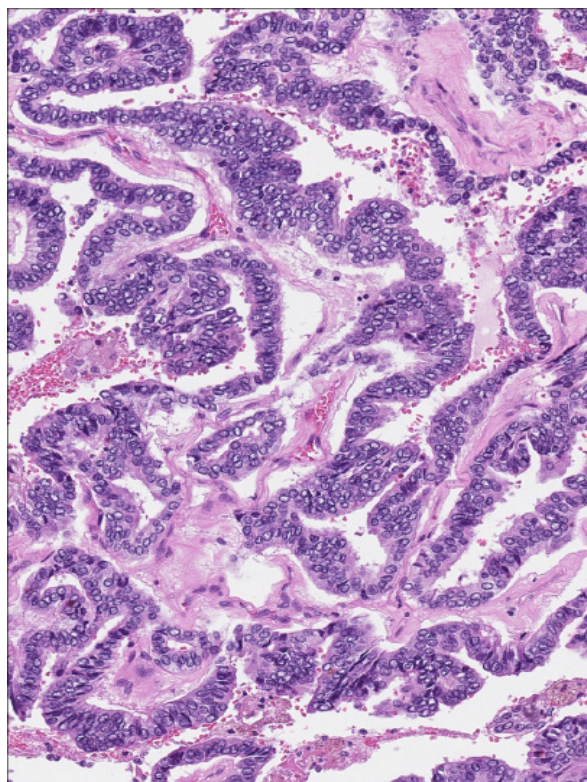


Figure 6: Neoplastic epithelium with overlapping, vesicular, irregular nuclei, typical for papillary thyroid carcinoma (Photomicrograph, HE stain).

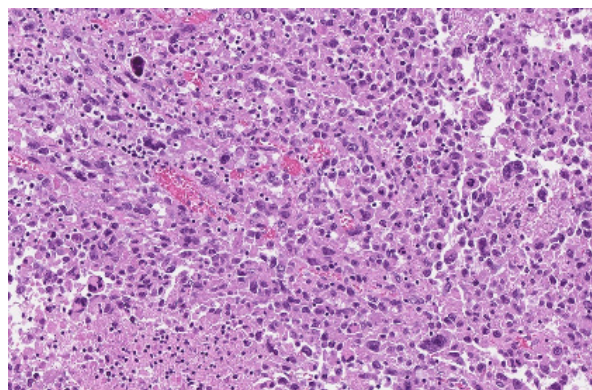


Figure 7: Large epithelioid cells, eosinophilic cytoplasm, polymorphic nuclei - necrosis, apoptotic, mitotic figures (Photomicrograph, HE stain).

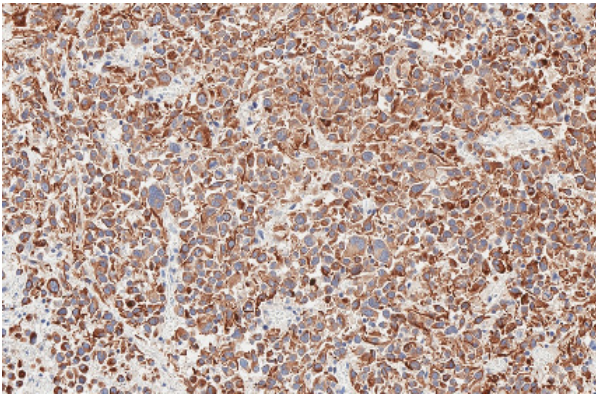


Figure 8: High-grade tumour component reactive for Cam5.2 (picture), Pan-Cytokeratin and CD56 (not shown), (Photomicrograph, Cam5.2 stain).

Discussion

Anaplastic thyroid carcinoma is known as a very rare and lethal thyroid cancer [1,3,6]. Little is known about ATC in the extrathyroidal area. The origin of retroperitoneal cancer with anaplastic transformation can be explained as a primary thyroid cancer with anaplastic transformation, as a struma ovarii with malignant transformation and metastases to the retroperitoneal area, as a metastases of papillary cancer with anaplastic transformation when a primary tumour is found in the thyroid or as a retroperitoneal monodermal teratoma composed of papillary cancer with anaplastic transformation [31]. We presented a very unique example of primary retroperitoneal cancer with ATC differentiation but there are known several other similar cases. One published case represents a 75-year-old male who had ATC developed between the sternocleidomastoid muscle and the common carotid artery. The thyroid had no changes and it was totally separated from the tumour. The biopsy of the thyroid or total thyroidectomy was not performed and histological analysis was not done. Possibly the ATC transformed from papillary thyroid carcinoma to an extrathyroidal tumour. Despite known poor survival, the patient lived 3.5 years without incidence of tumour recurrence after total resection and around 5 years after the first symptoms [17]. Another studied case of ATC manifestation in the extrathyroidal area was about a 63-year-old female. She complained about a rapidly growing abdominal mass during a month period and increased in size neck mass over a week which caused dysphagia, shortness of breath, and hoarseness. Important to note is that she had a history of goiter. The patient was diagnosed with ATC metastases in the abdominal subcutaneous fat layer, and lungs. Palliative radiotherapy was initiated for the neck area, and later systemic chemotherapy was administrated. However, due to the aggressive nature of ATC, the patient experienced vocal cord paralysis with severe airway problems and died around 9 weeks after the hospitalization because of respiratory distress [32]. A similar situation was seen in a 64 year-old male who was examined due to growing abdominal mass that was causing a mass effect on the stomach, left adrenal gland, kidney, and pancreas. The patient experienced total thyroidectomy 30 years ago because of papillary thyroid carcinoma and had an adjuvant radioactive iodine treatment. Later metastases in the cervical lymph nodes and left axilla were detected. The biopsy was taken from the growing retroperitoneal mass. According to the immunohistochemical profile, the results were similar to anaplastic transformation in metastatic papillary thyroid cancer. The patient had a palliative resection surgery and died 3 weeks after the operation because of large bowel obstruction and sepsis [33].

ATC is associated with high aggressiveness because of fast growth, high tendency for invasiveness, and low responsiveness to most therapies [5,6]. ATC cases are staged as IV-stage thyroid cancer due to ATC's very aggressive nature as is followed by the American Joint Committee on Cancer (AJCC) guidelines. Based on the invasion, the extent of the tumour, and distant metastases, ATC is divided into stages: IVA stage (T1T3a, N0, M0) is a tumour localized to the thyroid gland without lymph node involvement (N0) and distant metastasis (M0). Stage IVB represents a primary tumour with gross extrathyroidal extension (T3b,T4), and possible involvement of locoregional lymph nodes (\geq N1). IVC stage (any T, any N, M1) is a tumour with distant metastases (M1) [8].

Fine needle aspiration biopsy of a rapidly growing thyroid or any other extrathyroidal mass or an abnormal lymph node is the best method to diagnose ATC. However, it is difficult to detect ATC in the early stage. Mostly ATC is diagnosed in an advanced stage, being a big mass, compressing surrounding structures like the trachea and causing symptoms such as dyspnoea, dysphagia, neck pain, hoarseness, or other [2,8,22]. Nevertheless, ATC can also be detected incidentally during routine physical examination or urgent operations [2].

ATC is usually detected in older patients over 60 years [2,8,18,23]. Also, it is more common in women than in men [8,17,18,23]. Other known possible risk factors of this cancer are obesity, a history of known thyroid nodular disease, and malignancy in other sites such as prostate adenocarcinoma, uterine cancer, and colic gastrointestinal stromal tumours [15]. There are more known factors that influence the survival of patients like distant metastases, socioeconomic status, and treatment strategy [2,8,15,19]. Local invasion is usually seen in ATC cases. Also it is very common to detect metastasis in local or distant lymph nodes, lungs, liver, and bones [15,16,22,24,25].

The aetiology of ATC is still unknown [2,9]. There are several hypotheses: it arises de novo or from the same mass of differentiated or poorly differentiated thyroid carcinoma [3,6,10]. Histological analysis of ATC is difficult since it is composed of undifferentiated thyroid follicular cells and is likely to appear in a multitude of microscopic variations [6,13,16]. Various immunohistochemical and ultrastructural analysis are made to determine their epithelial origin [15]. As for all malignant tumours ATC has some certain features of high malignancy: invasiveness, extensive tumour necrosis, marked nuclear pleomorphism, and high mitotic activity [16,26]. The cell phenotype is known to be of the epithelial-mesenchymal transition type [1]. Morphology of the cells might be different: pleomorphic giant, spindled and squamous [16,27]. Also in some ATC cases paucicellular, rhabdoid or small cell variants can be found [16,26]. All of this makes ATC diagnosis more difficult and delayed [27]. Moreover, an association has been found between ATC and accumulated genetic alterations that are responsible for the regulation of the MAPK and PI3K/AKT signalling pathways. These pathways affect BARE, KRAS, PTEN and other genes that are known for several modulatory cell functions: growth, survival and proliferation [9,10].

The survival rate of ATC is very poor. According to the Research Consortium of Japan, the median OS survival of the IVA, IVB and IVC groups of patients was 15.8, 6.1, and 2.8 months respectively [11]. Surgical resection, radiation therapy, chemotherapy, or a combination of different treatment options are used for ATC patients [8]. The treatment strategy is known as one of the main factors to predict prognosis [19]. Better survival is seen in cases

after total resection of cancer with the combination of radiation therapy chemotherapy/targeted therapy [12,23,28]. A multimodal approach is particularly recommended for IVA and IVB stages. Palliative care and clinical trial are more often the treatment of choice for IVC stages [8]. The importance of the surgical approach was shown in a retrospective review, 1-year survival is much higher after total resection: 54% patients survived after total resection of primary cancer, 28% – residual resection and 8 % without surgery [13]. A retrospective study from Finland showed similar results. The median survival of patients with ATC was 3.1 months. Longer survival was seen in the radical surgery group than palliative, 11.6 and 3.2 months respectively. Also, multimodal approach determined longer median survival (11.8 months) [29]. Historically doxorubicin was the most used agent in chemotherapy for ATC treatment but new radiosensitizing agents such as taxanes (paclitaxel or docetaxel), platin, cisplatin, and carboplatin seem to be more effective and can be used alone or in combination [8]. In addition, these chemotherapy agents are commonly used with radiation therapy [28]. Results of molecular studies and the increased use of Tyrosine Kinase Inhibitor (TKI) therapy are also giving promising results. According to the study of Park et al. 2021, the multimodal approach of surgery, radiotherapy, and TKI therapy is the most effective and resulting in a median survival of 34.3 months and in a 6-month survival rate of 77.8%. Also, it is highlighted that more than half of the patients showed a good response rate in the group treated only with TKI therapy [30]. Other treatment methods like thyroid stimulating hormone suppression or radioiodine treatment are ineffective in ATC cases because this cancer does not produce thyroglobulin and does not uptake iodine. Therefore there are no tumour markers for ATC [3]. The treatment plan of patients with ATC is recommended to be managed by a multidisciplinary team of endocrinologists, oncologists, surgeons, radiotherapists, radiologists and psychologists [3,20]. Moreover personalized multimodal course of treatment seems to be the best approach for these patients [21].

Despite the improved prognosis of ATC over the past years because of target therapy, immunotherapy and combination of various treatment options, ATC remains a lethal disease [19,20,28]. It is thought that airway problems and failures of distant metastases control are one of the main causes of death for ATC patients [30].

Conclusion

Anaplastic thyroid carcinoma is a very rare type of cancer. Various factors such as metastatic stage, age, socioeconomic status, treatment possibilities influence the prognosis. Multimodal approach and personalised treatment are recommended for all anaplastic thyroid carcinoma. There are several clinical cases of extrathyroidal tumours with anaplastic thyroid carcinoma differentiation. Our presented case represents a very rare occurrence of anaplastic thyroid carcinoma in the retroperitoneal area. Even though almost 2 years have passed after the initial diagnosis, the patient is still alive and represents a better survival than is described in the literature. However, anaplastic thyroid carcinoma is a lethal disease and further studies are needed for a better management and survival enhancement.

Declarations

Ethics approval and consent to participate: Ethics approval was obtained and informed consent was gained from the patient.

Consent for publication: Consent for publication was gained from the patient.

Availability of data and materials: The dataset supporting the conclusions of this article is included within the article and its additional files.

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Authors' contributions:

1. Ugne Imbrasaitė - Investigation, Writing - original draft, Visualization, Writing - Review & Editing, Resources.
2. Augustas Beisa - Conceptualization, Writing - Review & Editing, Supervision.
3. Raminta Luksaite-Lukste - Review & Editing, Imaging analysis description.
4. Dmitrij Seinina - Review & Editing, Imaging analysis description.
5. Laurynas Berzanskas - Writing - Review & Editing, Imaging analysis - Description, Resources.
6. Pranas Serpytis - Review & Editing.
7. Tomas Poskus - Writing - Review & Editing, Supervision.

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