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SECONDARY PAPILLARY THYROID CARCINOMA IN A NON-IRRADIATED PEDIATRIC LEUKEMIA SURVIVOR: CRITICAL IMPLICATIONS FOR ADVANCED NURSING SURVEILLANCE AND LONG-TERM SURVIVORSHIP PARADIGMS

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ABSTRACT

Objectives: This case study aims to document an extraordinary instance of early-onset secondary papillary thyroid carcinoma (PTC) in a non-irradiated pediatric survivor of acute lymphoblastic leukemia (ALL) and to evaluate its implications for advanced oncology nursing surveillance models.
Methods: A descriptive, retrospective single-patient case study design was utilized. Clinical data, including multi-agent chemotherapy dosing protocols (ALL-IC BFM 2009), diagnostic radiologic logs, pre-operative thyroid function assays, and high-resolution ultrasonography parameters, were critically reviewed alongside post-operative histopathological data.
Key Findings: A 3.5-year-old boy achieved molecular remission from B-cell ALL after exclusive chemotherapy, without any cranial or cervical irradiation. Remarkably, only 36 months post-primary diagnosis, proactive nursing physical palpation during a routine follow-up incidentally detected a firm cervical mass. High-resolution ultrasonography and fine-needle aspiration biopsy confirmed a metastatic classical variant of PTC (pT1bN1bM0). The patient successfully underwent a total thyroidectomy and modified cervical lymphadenectomy, achieving stable clinical remission over an 18-month longitudinal observation period.
Conclusions: Secondary metastatic PTC can manifest exceptionally early in pediatric leukemia survivors, completely independent of prior exposure to ionizing radiation. This rapid oncogenesis challenges radiation-centric surveillance paradigms. To prevent diagnostic delays, we recommend the integration of regular, standardized manual thyroid palpation into routine nursing assessments for all pediatric oncology survivors. Future research must prioritize multi-center registries and routine molecular profiling to define chemotherapy-induced genotoxic thresholds and uncover underlying somatic-germline interactions in very young cohorts.

KEYWORDS

Pediatric Acute Lymphoblastic Leukemia, Papillary Thyroid Carcinoma, Secondary Primary Malignancy, Nursing Surveillance, Survivorship Care, Cytotoxic Genotoxicity

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1. Introduction:

The therapeutic paradigm of pediatric hemato-oncology has undergone a remarkable evolution over the past four decades. The introduction of risk-stratified, multi-agent chemotherapy protocols, combined with sophisticated supportive care, has transformed pediatric acute lymphoblastic leukemia (ALL)—once a universally fatal disease—into a highly curable malignancy with five-year survival rates now comfortably exceeding ninety percent in high-income healthcare jurisdictions (Tsinopoulou et al., 2025). Paradoxically, this monumental achievement in oncology has introduced a complex public health challenge: the management of a growing cohort of childhood cancer survivors who are uniquely predisposed to severe, lifelong treatment-related sequelae. Among these long-term morbidities, the emergence of subsequent secondary primary malignancies (SPMs) represents the most devastating complication, carrying a disproportionately high rate of excess late mortality (Dixon et al., 2023; Westerveld et al., 2024).

The human thyroid gland has long been recognized as an organ with exquisite susceptibility to oncogenic transformation following external insults. For decades, the prevailing medical consensus has established thyroid carcinoma as a hallmark secondary solid tumor almost exclusively linked to the delivery of ionizing radiation (Cherella & Wassner, 2022). Survivors of Hodgkin lymphoma, brain tumors, or those who underwent cranial and spinal irradiation or total body irradiation (TBI) as part of a conditioning regimen for hematopoietic stem cell transplantation have historically comprised the primary high-risk cohorts. Radiation-induced thyroid cancer typically features a prolonged latency period, with the majority of secondary neoplasms emerging between seven to fifteen years post-exposure, and rarely before five years.

Now, however, large-scale registries, including the Childhood Cancer Survivor Study (CCSS), are actively challenging this long-held radiation-centric dogma. There is a small but statistically significant and rising incidence of thyroid neoplasms being documented in survivors of childhood ALL who were never exposed to therapeutic radiation (Clement et al., 2020). This shifting clinical landscape strongly implies that the biological vulnerability of the pediatric thyroid gland extends far beyond radiological damage. Instead, it points toward a multifactorial etiology involving systemic cytotoxic stress, genomic instability, and targeted organ damage induced by intensive combinations of chemotherapeutic agents, such as alkylating substances and anthracyclines.

From both a clinical oncology standpoint and an advanced healthcare management perspective, the case detailed in this report is of extraordinary significance. It involves an extremely young patient (3.5 years old at primary diagnosis) who developed a metastatic, classic variant of papillary thyroid carcinoma (PTC) after a phenomenally compressed latency period of only three years following the onset of ALL, without a single gray of therapeutic radiation. Such an accelerated oncogenic timeline directly subverts established screening guidelines, which typically defer aggressive solid tumor surveillance until at least a decade of survivorship has elapsed (Birenboim & Rabinowicz, 2025).

This case study is therefore designed to delve deeply into the underlying clinical mechanism, the critical diagnostic traps encountered during routine follow-ups, and the profound practical implications for advanced nursing practice. It emphasizes that oncology nurses, who serve as the frontline coordinators of survivorship care, must possess the specialized clinical acumen to detect early-stage deviant pathologies, thereby driving a necessary re-evaluation of long-term surveillance care plans.

2. Methodology:

To rigorously evaluate this highly atypical clinical presentation and extract actionable insights for innovative health delivery and nursing management, a descriptive, retrospective, single-patient case study design was executed. This methodological approach allowed for an exhaustive, longitudinal investigation of the patient's clinical course, integrating primary oncological treatment parameters, secondary diagnostic screening technologies, surgical pathology, and subsequent multidisciplinary survivorship protocols.

2.1. Data Collection and Sources

A thorough review of the patient's comprehensive electronic health records (EHR) was conducted. Data extraction parameters included precise cumulative chemotherapy dosing calculations, diagnostic radiologic exposure logs, laboratory assays, serial nursing physical assessment notes, pre-operative imaging data, cytopathology reports, and final post-operative histopathological classifications. The care trajectory was tracked continuously from the initial day of leukemia presentation through to the post-thyroidectomy follow-up period.

2.2. Diagnostic Technologies and Evaluated Instruments

The identification and staging of the secondary primary malignancy relied upon three highly standardized clinical and technological modalities:

1. **High-Resolution Real-Time Ultrasonography (US):** Executed using a premium ultrasound system equipped with a high-frequency linear transducer (12–15 MHz). This modality was evaluated for its utility in differentiating benign reactive lymphadenopathy from malignant cervical structures, utilizing the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) criteria adapted for pediatric cohorts.
2. **Fine-Needle Aspiration Biopsy (FNAB):** Performed under continuous, real-time ultrasound guidance using a 25-gauge needle. The resulting cytological smears were fixed, stained, and systematically classified utilizing the standardized criteria of *The Bethesda System for Reporting Thyroid Cytopathology*.
3. **Histopathological Analysis:** Post-surgical tissue specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 4 micrometers, and stained with hematoxylin and eosin (H&E). Staging was determined based on the American Joint Committee on Cancer (AJCC) TNM staging system for thyroid carcinoma.

2.3. Ethical Considerations and Patient Privacy

This investigation adhered strictly to the ethical standards established by the 1964 Declaration of Helsinki and its subsequent amendments. In full accordance with the statutory regulations outlined by the Bioethics Committee of Poland, formal institutional review board (IRB) approval was determined to be exempt, given that this study constitutes a retrospective, non-interventional analysis of an individual patient utilizing completely de-identified, standard-of-care clinical data, with zero experimental procedures.

Prior to manuscript compilation, comprehensive, written informed consent was explicitly obtained from the patient's legal guardians (his parents). This consent covered the academic use of clinical histories, laboratory results, and ultrasound images. To guarantee absolute anonymity and uphold the highest standards of data privacy, all personal identifiable information (PII), specific geographic clinical locations, and exact calendar dates were thoroughly removed or masked.

3. Case Presentation:

3.1. Primary Diagnosis, Leukemia Therapy, and Comprehensive Clinical Data

In the late autumn, a 3.5-year-old boy with no significant prior medical history or known familial history of early-onset malignancy was admitted to a tertiary pediatric hematology department. The child's presentation was marked by a three-week clinical history of persistent, migratory bone pain that severely limited his mobility, intermittent low-grade pyrexia, progressive pallor, and recurrent, painful oral aphthous ulcers.

Upon initial clinical presentation, physical examination revealed profound generalized lymphadenopathy (bilateral cervical, axillary, and inguinal nodes measuring up to 1.5 cm) and moderate hepatosplenomegaly. Initial laboratory evaluation demonstrated a critical hematological profile: a profound leukocytosis with a white blood cell count of 64.2 x 10^9/L, a severe normocytic anemia with a hemoglobin level of 6.8 g/dL, and a marked thrombocytopenia with a platelet count of 32 x 10^9/L. The peripheral blood smear revealed a blast count of forty percent.

A subsequent bone marrow aspiration was performed, demonstrating a hypercellular marrow completely packed with uniform, small-to-medium-sized lymphoblasts. Flow cytometric immunophenotyping of the bone marrow aspirate conclusively confirmed a diagnosis of common B-cell acute lymphoblastic leukemia (ALL), with the blasts expressing CD19, CD10, CD22, and terminal deoxynucleotidyl transferase (TdT), while remaining negative for myeloid and T-lineage markers. Cytogenetic analysis via fluorescent in situ hybridization (FISH) demonstrated a normal diploid karyotype without the presence of the t(12;21) ETV6-RUNX1 or t(9;22) BCR-ABL1 translocations.

The patient was stratified into the standard-risk arm of the international ALL-IC BFM 2009 treatment protocol. He immediately commenced an intensive, multi-phase cytotoxic regimen:

- **Protocol I (Induction Phase):** Consisted of systemic prednisone (60 mg/m2/day orally), weekly intravenous vincristine (1.5 mg/m2), intravenous daunorubicin (30 mg/m2 per dose; cumulative dose of 120 mg/m2), and repeated administrations of native L-asparaginase (10,000 U/m2 per dose), coupled with age-adjusted intrathecal methotrexate to prevent central nervous system relapse.
- **Protocol M (Consolidation Phase):** Incorporated four courses of high-dose intravenous methotrexate (5 g/m2 administered as a 24-hour continuous infusion) with leucovorin rescue, oral 6-mercaptopurine, and a critical dose of cyclophosphamide (1000 mg/m2 split across two doses).
- **Protocol II (Re-induction Phase):** Re-exposed the patient to dexamethasone, vincristine, doxorubicin (30 mg/m2 per dose; cumulative dose of 60 mg/m2), and a second exposure to cyclophosphamide (1000 mg/m2).
- **Maintenance Therapy:** Completed via daily oral 6-mercaptopurine and weekly oral methotrexate over a prolonged period, terminating after a total treatment duration of two full years.

A defining and crucial parameter of this patient's medical history is the **absolute avoidance of cranial, cervical, or total body irradiation** at any juncture of his therapeutic journey. Furthermore, his cumulative exposure to diagnostic ionizing radiation was strictly monitored, kept to an absolute minimum, and limited exclusively to four standard chest radiographs and non-ionizing abdominal/pelvic ultrasounds. The patient tolerated the chemotherapy exceptionally well, achieving a complete morphological and minimal residual disease (MRD)-negative molecular remission by day 33 of induction, which was successfully sustained throughout the entire maintenance phase.

3.2. Secondary Oncogenesis, Diagnostic Trajectory, and Pre-Operative Assessment

Approximately thirty-six months after the initial diagnosis of leukemia, and just one year after the complete cessation of all maintenance chemotherapy, the patient—now 6.5 years old—was brought to the pediatric oncology clinic for a scheduled, routine survivorship follow-up appointment. Coincidentally, the child had developed mild symptoms of rhinitis and a clear nasal discharge over the preceding forty-eight hours, consistent with an acute upper respiratory viral infection.

During the comprehensive physical examination, an advanced oncology nurse practitioner executed a meticulous palpation of the cervical lymph node chains. While assessing the left side of the neck, the nurse

identified a distinct, firm, non-tender, and non-mobile mass localized within the deep cervical chain, specifically at level III. The mass did not shift visibly with deglutition.

In a standard pediatric setting, isolated cervical lymphadenopathy in a child exhibiting concurrent viral rhinitis is overwhelmingly classified as benign reactive hyperplasia, often managed with conservative clinical observation. However, the nurse practitioner, operating with a high index of oncological suspicion fueled by the patient's history of intense systemic chemotherapy, refused to dismiss the finding. Recognizing the firm texture and lack of mobility as clinical red flags, the nursing staff immediately bypassed the standard observational window and ordered an urgent, high-resolution diagnostic neck ultrasound.

The high-resolution ultrasonographic evaluation of the neck yielded deeply alarming structural results:

- **Left Thyroid Lobe:** Demonstrated a distinct, solitary, solid nodule measuring 12.5 mm in its maximum diameter. The nodule was distinctly hypoechoic compared to the surrounding normal thyroid parenchyma and exhibited a highly suspicious "taller-than-wide" morphology, irregular, microlobulated margins, and a complete absence of a peripheral halo.
- **Internal Architecture:** The nodule was packed with multiple, punctate echogenic foci measuring less than 1 mm, casting no acoustic shadows—findings highly diagnostic of psammomatous microcalcifications (Francis et al., 2015).
- **Vascularity & Lymph Nodes:** Color Doppler imaging mapped out a chaotic, intense central hypervascularity. Evaluation of the left level II, III, and IV cervical compartments identified several enlarged, rounded lymph nodes with a total loss of the normal echogenic fatty hilum and early subcapsular microcystic/cystic changes.

To ensure complete systemic and metabolic safety prior to surgical intervention, comprehensive baseline laboratory testing was conducted:

- **Thyroid Function Profile:** Serum Thyroid-Stimulating Hormone (TSH) was measured at 2.1 mIU/L (normal reference range: 0.5–4.5 mIU/L), and Free Thyroxine (FT4) was 14.8 pmol/L (normal reference range: 10.0–22.0 pmol/L), confirming a strict euthyroid metabolic state.
- **Oncological Biomarkers:** Baseline serum Thyroglobulin (Tg) was significantly elevated at 142.0 ng/mL (normal reference: less than 35 ng/mL), serving as a crucial baseline marker for subsequent long-term recurrence surveillance. Anti-thyroglobulin antibodies (TgAb) were negative, verifying the technical validity of the Tg assay.

3.3. Surgical Intervention, Pathology, and Post-Operative Longitudinal Observation

Given the high-risk ultrasound profile, the patient underwent an ultrasound-guided fine-needle aspiration biopsy (FNAB). The cytological evaluation of the thyroid aspirate definitively classified the lesion as **Bethesda Category VI (Malignant)**, explicitly diagnostic of papillary thyroid carcinoma.

The patient was promptly transferred to a specialized pediatric endocrine surgery unit, where a total thyroidectomy combined with a therapeutic modified left-sided radical cervical lymphadenectomy (encompassing levels II, III, IV, and V) was performed. The final macroscopic and microscopic histopathological analysis confirmed a classic variant of papillary thyroid carcinoma originating in the left lobe, measuring 13 mm in its greatest dimension, with focal extrathyroidal extension into the immediate perithyroidal adipose tissue. Regional metastatic involvement was confirmed in four out of the eighteen successfully retrieved lymph nodes, resulting in a final pathological stage of **pT1b N1b M0 (Stage I)**.

Following the surgical intervention, the patient was initiated on suppressive doses of levothyroxine (100 mcg/day orally) to maintain serum TSH levels below 0.1 mIU/L. Six weeks post-surgery, therapeutic radioactive iodine (131-I) ablation was successfully administered at a dose of 1.11 GBq (30 mCi).

The patient has since been followed closely within our specialized survivorship program for an uninterrupted **post-operative longitudinal observation period of 18 months**. Serial follow-up high-resolution neck ultrasounds performed at 3, 6, 12, and 18 months have demonstrated a completely clean surgical bed with no structural evidence of local recurrence or contralateral nodular development. Stimulated serum Thyroglobulin levels dropped sharply from the pre-operative baseline, remaining completely undetectable (less than 0.1 ng/mL) alongside negative TgAb titers, confirming a highly stable and successful complete clinical remission.

4. Discussion:

4.1. Broadening the Literature Landscape and Systemic Pathophysiology

The manifestation of a highly aggressive, metastatic classic variant of papillary thyroid carcinoma in a 6.5-year-old child after an incredibly brief latency period of only thirty-six months post-leukemia diagnosis represents a clinical anomaly of the highest order. It fundamentally upends established oncological timelines.

In the vast majority of documented pediatric cohorts, secondary thyroid cancer is heavily associated with prior external beam radiation therapy, exhibiting a protracted latency window that typically spans seven to fifteen years (Dixon et al., 2023; Tsinopoulou et al., 2025). Cases emerging under five years are rare, and cases developing within 36 months in an absolute non-irradiated field are profoundly exceptional. To contextualize this event within the broader literature, large-scale studies such as the Childhood Cancer Survivor Study (CCSS) have demonstrated that while the relative risk of thyroid cancer is highest after radiation, survivors treated exclusively with high-dose chemotherapy also exhibit an elevated risk compared to the general population (Clement et al., 2020).

In the complete absence of therapeutic ionizing radiation, scientific and pathophysiological focus must shift toward the cumulative genotoxic potential of multi-agent systemic chemotherapy. The ALL-IC BFM 2009 protocol utilizes a highly intensive delivery of alkylating agents (cyclophosphamide) and anthracyclines (daunorubicin and doxorubicin). Alkylating agents achieve cytotoxicity by cross-linking DNA strands, inducing alkylation at the N7 position of guanine, which results in severe DNA mispairing and strand breaks. Anthracyclines intercalate between base pairs and inhibit topoisomerase II, preventing the re-ligation of DNA strands and generating a massive intracellular cascade of reactive oxygen species (ROS) that induces profound oxidative DNA damage (Clement et al., 2020; Tian et al., 2023).

While these mechanisms are highly effective at eradicating malignant lymphoblasts, they also inflict severe, non-targeted collateral damage upon healthy, rapidly dividing somatic tissues. The pediatric thyroid gland, characterized by active cellular proliferation and physiological growth during early childhood, is uniquely vulnerable to this systemic genotoxic assault. We hypothesize that the intense combination of cyclophosphamide and anthracyclines induced profound double-strand DNA breaks and altered DNA repair mechanisms within the thyroid follicular epithelium. This accelerated genomic instability bypassed the standard multi-decade latency period, driving rapid neoplastic transformation and early metastatic dissemination to regional lymph nodes.

Furthermore, recent oncogenetic literature suggests that chemotherapy-induced oxidative stress may accelerate somatic mutations within the mitogen-activated protein kinase (MAPK/ERK) signaling pathway, such as *BRAF* mutations or *RET/PTC* rearrangements, which are hallmarks of classic pediatric PTC pathogenesis (Cherella & Wassner, 2022).

4.2. A Balanced Synthesis of Clinical and Operational Implications

This case exposes a perilous diagnostic trap that could have easily resulted in a catastrophic delay in diagnosis. In pediatric medicine, cervical lymphadenopathy is an ubiquitous, everyday finding, almost always representing benign reactive follicular hyperplasia secondary to common childhood viral infections—such as the mild rhinitis presented by our patient. However, in a child with a history of intensive cytotoxic therapy, the standard clinical heuristic must change.

The fact that this nodule was detected at an early, treatable stage is entirely attributable to the advanced clinical skills and high index of suspicion maintained by the oncology nursing staff. By recognizing that the firm, non-tender, fixed texture of the cervical mass was highly uncharacteristic of viral reactive lymphadenopathy, the nursing team correctly initiated an immediate escalation of care via high-resolution ultrasonography.

To ensure this case delivers pragmatic utility for healthcare systems, its practical implications must be framed with operational balance. While it is tempting to recommend universal, high-frequency ultrasound screening for all pediatric cancer survivors, such an aggressive approach would inevitably trigger an unsustainable surge in healthcare expenditures, high rates of false-positive findings, unnecessary fine-needle biopsies, and severe psychological distress for families.

Therefore, a more balanced and cost-effective clinical model involves the implementation of **targeted, nursing-led physical surveillance protocols**. Instead of relying on universal imaging, survivorship clinics should enforce mandatory, highly structured, manual thyroid palpation and cervical lymph node mapping during every routine follow-up. Ultrasound imaging should not be used indiscriminately, but rather reserved as an immediate, secondary escalation tool triggered exclusively by specific clinical "red flags," such as localized tissue induration, asymmetry, or node immobility that persists beyond standard infectious windows. This tiered approach effectively optimizes clinical vigilance while safeguarding healthcare resources and preventing over-diagnosis.

4.3. Defining the Knowledge Gap and Future Research Directions

Despite the successful clinical resolution of this patient's secondary malignancy, this case directly highlights several profound gaps in current medical and scientific knowledge that remain completely unresolved:

- **The Absence of Long-Term Non-Irradiated Data:** The current body of literature lacks robust, long-term longitudinal data regarding the true cumulative incidence of solid secondary tumors in patients who were treated with modern, intensive chemotherapy but completely spared from radiation. Most historical survivorship cohorts are heavily skewed toward older protocols that combined both modalities, leaving the exact oncogenic potential of chemotherapy alone poorly defined.
- **Lack of Clear Dosimetric/Genotoxic Thresholds:** There are currently no established dosimetric thresholds or linear risk models that can correlate specific cumulative doses of alkylating agents or anthracyclines with the precise mathematical probability of secondary thyroid tissue transformation. It remains entirely unknown why certain children develop rapid genomic instability at standard protocols while others remain unaffected.
- **Undefined Role of Somatic-Germline Interactions:** A significant limitation of current clinical practice—including the present report—is the lack of routine, accessible germline and somatic molecular profiling at the time of primary cancer diagnosis. The exact interplay between standard cytotoxic chemotherapy and underlying genetic risk syndromes (such as *TP53* or *DICER1* variants) remains largely theoretical in very young cohorts.

To bridge these critical knowledge gaps, the international oncology community must move beyond isolated case reports and prioritize the following **future research directions**:

1. **Establishment of Multi-Center Registries:** Large-scale, international collaborative registries must be developed to track non-irradiated childhood cancer survivors, specifically isolating chemotherapy-only protocols to map the true long-term incidence of secondary solid tumors.
2. **Routine Biobanking and Molecular Profiling:** Incorporating routine genomic sequencing and biobanking at the entry point of survivorship care will allow researchers to identify specific genetic biomarkers that predispose children to rapid, chemotherapy-induced oncogenesis.
3. **Prospective Screening Trials:** Prospective, randomized clinical trials are urgently needed to evaluate the long-term cost-benefit and psychological impact of structured physical palpation protocols versus targeted, low-threshold ultrasonography in vulnerable pediatric cohorts.

5. Conclusion:

This highly unusual case report demonstrates that secondary metastatic papillary thyroid carcinoma can manifest exceptionally early in the survivorship trajectory of pediatric leukemia patients, completely independent of prior exposure to ionizing radiation. The rapid, three-year emergence of this secondary tumor exposes the critical limitations of contemporary, radiation-centric surveillance guidelines and challenges the medical community to implement a profound paradigm shift in long-term follow-up care.

To translate these findings into concrete, balanced clinical practice, we propose the following systematic recommendations:

- **Mandatory Physical Surveillance:** Integration of regular, standardized manual thyroid palpation and meticulous cervical lymph node mapping into every routine follow-up visit for all pediatric oncology survivors, completely irrespective of their primary treatment modality or radiation status.
- **Frontline Nursing Empowerment:** Development of specialized, nursing-led physical assessment protocols within survivorship clinics, ensuring that advanced practice nurses have the diagnostic autonomy to immediately escalate care to high-resolution neck ultrasounds upon the detection of any abnormal, indurated, or fixed cervical structures.
- **Early Genetic Integration:** Routine deployment of genetic counseling and comprehensive germline mutational screening for any pediatric patient presenting with early-onset secondary solid tumors, utilizing these molecular insights to bridge current gaps in risk stratification.
- **Proactive Family Education:** Enhanced, nurse-led educational interventions aimed at parents and survivors to explicitly convey the long-term genotoxic risks of systemic chemotherapy, thereby optimizing long-term adherence to surveillance care plans and ultimately transforming the prognosis of this uniquely vulnerable patient population.

Declarations & Disclosures:

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Ethical Approval: The study was conducted in strict accordance with the ethical tenets of the Declaration of Helsinki. According to the current statutory regulations of the Bioethics Committee of Poland, formal institutional committee approval was not required, as this work represents a retrospective analysis of completely anonymized, standard clinical procedures with no experimental components.

Conflicts of Interest: The authors explicitly declare no conflicts of interest to declare.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

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