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Elevations of α-fetoprotein in patients undergoing chemotherapy for pure testicular seminoma: a retrospective cohort study

Seán J. Costelloe[1,2*], Jennifer D. Spencer[1], Kathryn Humphries[3], Daniel Stark[3] and Elaine Dunwoodie[3]

Abstract

Background α-Fetoprotein (AFP) is conventionally absent in testicular classical seminoma (TCS). However, moderate AFP elevations can occur in TCS patients, as observed at this and other centres, which can be challenging to diagnostic and management practices.

Methods This retrospective cohort study considered AFP concentration in the context of germ-cell tumour diagnosis and characterisation at baseline (BL), disease status during chemotherapy, and long-term surveillance. The study considered patients with histologically diagnosed stage 1 TCS requiring chemotherapy over six years. For those with AFP above the reference interval at BL, histological imaging, case notes, and biochemical data were reviewed from BL to surveillance completion. Outcomes included AFP changes, diagnoses, therapy, disease progression, and death.

Results Of the 175 patients included, eight (4.6%) had elevated AFP at BL. Of these, two showed statistically but not clinically significant AFP changes during therapy, while six had moderate, stable AFP elevations with no changes in diagnosis during follow-up. During therapy, one patient developed metastases, and one died of causes likely unrelated to their TCS.

Conclusions Mild elevations of AFP in TCS may lead to diagnostic uncertainty or inappropriate management and investigation. However, AFP changes, alongside imaging, did not affect diagnosis, therapy, or follow-up at this centre for any of the patients examined. A subgroup of TCS patients has stable, moderate AFP elevations unrelated to tumour aetiology.

Keywords A-fetoprotein, Outcome, Prognosis, Testicular seminoma

*Correspondence:
Seán J. Costelloe
sean.costelloe@hse.ie
[1]Blood Sciences, Old Medical School, The Leeds Teaching Hospitals NHS Trust, Thoresby Place, Leeds, UK
[2]Department of Clinical Biochemistry, Cork University Hospital, Wilton, Co. Cork, Republic of Ireland
[3]Department of Oncology, The Leeds Teaching Hospitals NHS Trust, Leeds, UK

Background

Testicular cancer (TC), most common in men aged 15–44 years (yr) old, accounts for approximately 1% of all male malignancies in the United Kingdom (UK) [1–7]. In the UK population, TCs are predominantly germ-cell tumours (GCTs) [4–7], and 45% of these, approximately 950 cases per year, are testicular classical seminomas (TCS) according to international classification systems [4, 6–9]. Tumour markers (TMs) aid the diagnosis, prognostication, monitoring of chemotherapy, and long-term surveillance of patients with GCTs [10], and elevations of α-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) have good positive predictive value for GCT in the context of a testicular lump [11].

Since it is secreted by cells of yolk sac origin, conventional wisdom holds that TCS does not produce AFP at detectable concentrations [12]. However, moderately elevated AFP has previously been observed in patients with confirmed histological diagnoses of TCS at this centre. Indeed, AFP elevation in TCS is a more widely recognised phenomenon, with the potential for misdiagnosis and mismanagement of patients [13–16]. Moderate AFP elevations in TCS patients are proposed to result from a combination of non-tumoral sources [17, 18], undetected yolk sac elements [19, 20], chemotherapy effects [21], or analytical variability [22], underscoring the need for cautious interpretation and further research. Clarifying the clinical significance of moderate AFP elevations in TCS is challenging. There is no consensus definition for 'moderate' AFP elevation, and centres may use different analytical platforms. Without guidelines, clinical decision limits for AFP are often based on expert opinion. Since AFP elevations are unexpected in TCS, the significance of moderate AFP elevations remains unclear. More precise guidelines are needed to determine whether these elevations should impact diagnosis or treatment.

AFP is also commonly used in the surveillance of TC patients for recurrent disease following definitive chemotherapy and regular monitoring following treatment for advanced TCS, although evidence for the clinical benefit of this practice is currently lacking.

This retrospective cohort study considers AFP concentrations from baseline (BL) until the completion of planned surveillance in chemotherapy patients, where the histological diagnosis is TCS. This study examines AFP levels in TCS patients at baseline and during follow-up to assess their diagnostic value and clinical implications. This study aims to inform clinicians of the thresholds and trends in AFP concentration that warrant careful consideration in TC, where the histological diagnosis is TCS.

Methods

Study design

This retrospective cohort study was conducted at the Leeds Cancer Centre (LCC), a tertiary referral centre for TC. Patients diagnosed with stage 1 TCS between 1st January 2008 and 31st December 2013 were included in the analysis. Using unique patient identifiers, data for these men were collected retrospectively from electronic health records, laboratory information systems and the electronic patient record at LCC. The study aimed to evaluate AFP concentrations and outcomes during chemotherapy and subsequent follow-up.

Patient population

Approximately 30 men per year requiring chemotherapy for stage 1 TCS are treated at LCC. TCS is defined as a seminoma confined to the testes, with no histological evidence of other forms of testicular cancer. The BL period was defined as the period from − 28 days up to and including the day of commencement of chemotherapy (Day 0). All eligible patients were retrospectively included in the study if they had confirmed stage 1 TCS either at BL or retrospectively; at least one AFP measurement at BL above the upper limit of the reference interval (ULRI); chemotherapy administered post-orchiectomy or for relapsed disease that was initially managed with surveillance.

Patients diagnosed with metastatic seminoma (stage IM or above), primary mediastinal, or retroperitoneal seminoma at baseline (by histology or imaging) were excluded from the study. These exclusions were implemented to maintain a focus on localised stage 1 testicular seminoma and ensure the integrity of AFP trend analyses. By excluding metastatic, mediastinal, and retroperitoneal seminomas, the study eliminates confounding factors related to advanced disease biology or non-gonadal origins, enabling a more accurate assessment of AFP concentration in the context of localised TCS. Patients are discussed using anonymised notations, such that "Patient X" is referred to as "P_X" and so on.

AFP measurement and statistical methods

AFP concentrations were measured using Siemens Centaur (pre-November 2018) and Atelica analysers at The Department of Blood Sciences of The Leeds Teaching Hospitals NHS Trust, and the agreement between the analysers is acceptable. The ULRI for AFP was 7 kIU/L, derived from a population of 780 individuals, encompassing 98.4% of the reference population (Siemens Healthcare). AFP concentrations between 8 and 14 kIU/L (1–2 * ULRI) were termed "moderate elevation" based on local expert consensus.

The reference change value (RCV) is a standard tool in laboratory medicine used to determine whether a change

in a biomarker exceeds the combined effects of intraindividual biological variability (CV_i) and assay imprecision (CV_a). The RCV for AFP was calculated using the formula ($2.8 * \sqrt{CVi^2 * CVa^2} = 2.8 * \sqrt{12.2^2 * 3.3^2} = 35.4\%$), where CV_i was 12.2% [23] and average CV_a was 3.3% for the AFP immunoassays. Changes exceeding the RCV are unlikely to be caused by variability or imprecision alone and may reflect a physiological or pathological process, such as a change in disease state and are termed "significant."

The AFP assays performed satisfactorily in the UK National External Quality Assurance Scheme for the study period. AFP frequency and CV_i were compared between seminoma patients and reference populations [24]. Descriptive statistics were used to summarise data on patient demographics, AFP trends, and treatment outcomes. All statistical analyses were performed in Excel and Analyse-IT.

Clinical assessments and follow-up

Each patient had AFP and human chorionic gonadotropin (hCG) levels measured at baseline, during chemotherapy, and periodically during post-treatment surveillance. Disease status was evaluated according to the Tumour-Node-Metastases (TNM) classification system for malignant tumours [25–27]. Patients entered a five-year surveillance program following the initiation of therapy, during which blood tests, chest X-rays, and computed tomography (CT) scans were conducted several times per year, as deemed clinically appropriate for each patient. Certain patients continued surveillance beyond five years upon the recommendation of the oncology team.

Patients were followed from the initiation of chemotherapy until June 2022. Data collected included patient age, chemotherapy regimens., histological and imaging findings at BL and during follow-up, and blood test results, including TMs. Outcomes considered were disease recurrence, all-cause mortality, and trends in AFP.

Ethics statement

This study complied with UK data protection legislation, including the Data Protection Act 2018 [28], and the Caldicott principles [29]. All patient records and laboratory results were accessed solely by clinicians and scientists directly involved in patient care. Patients were treated according to standard care protocols, and no interventions or modifications to their care were made as part of this study. To ensure confidentiality, all data were anonymised before analysis by removing direct patient identifiers and assigning unique study identifiers.

According to the NHS Health Research Authority's online decision-making tool for research ethics, a formal review by the NHS Research Ethics Committee (REC) was not required for this study, as it involved a retrospective review of fully anonymised patient data [30]. This determination aligns with UK guidelines for research ethics in studies involving anonymised health data.

To ensure compliance with UK data protection legislation and ethical standards, the authors consulted the Caldicott Guardian at Leeds Teaching Hospitals NHS Trust. The Caldicott Guardian confirmed that patient consent was not required as no additional data were collected and the study adhered to national legislation and guidelines. Furthermore, the Caldicott Guardian acknowledged the authors' clear understanding of their responsibilities under the UK GDPR, the Data Protection Act 2018, and the Caldicott principles, affirming their compliance with these standards during the collection and processing of patient data.

Results

Patients included in the analysis

Out of 175 men with an initial diagnosis of TCS and an AFP measurement at BL, 8 (4.6%) had confirmed stage 1 disease accompanied by moderately elevated AFP and were included as subjects in the analysis (Table 1). Subjects had a median age of 37 year at BL (interquartile range (IQR) = 12 year), and AFP was measured a median of 14 (IQR = 7.8) times for each patient in the BL and surveillance periods. Subjects had AFP measurements taken for a median period of 58.7 (IQR = 17.0) months (mo) following initiation of chemotherapy. Patient records were reviewed on 1st June 2022, allowing consideration of patient outcomes, and AFP concentrations (Fig. 1) over a median of 11.5 (IQR = 1.7) yr. The moderate elevations of AFP observed at BL did not affect their initial diagnosis or treatment.

Chemotherapy regimens for subjects included in the study

In the subjects, chemotherapy regimens were as follows: carboplatin (AUC7) only in five patients; carboplatin (AUC7) with para-aortic radiotherapy in one patient; and bleomycin, etoposide and platinum (BEP) in one patient (Table 1).

Follow-up of patients who had significant changes in AFP concentration during treatment

Two patients had significant changes in AFP concentration during treatment. Initially, P_1 was treated as stage 3 disease due to a mediastinal mass on imaging. There was no retroperitoneal involvement, but the patients had a prior history of seminoma in the contralateral testis, for which para-aortic radiotherapy had been given. As a result, he was treated with three cycles of BEP chemotherapy. The mass persisted on completion of treatment, and when resected six months after his final dose of chemotherapy, histology was consistent with

Table 1 Details for testicular classical seminoma patients with AFP elevations at baseline in this study. The table summarises the characteristics of the eight men included in this study as summarised in the text. Abbreviations used are as follows: α-fetoprotein (AFP), Baseline (BL), Chemotherapy (CTX), Diagnosis (Dx), Follow-up (FU), Metastases (Mets), millimetre (mm), Past Medical History (Hx), Patient Identifier (PID), Tumour-Node-Metastases classification (TNM), years (yr)

PID	Age (yr)	Hx	Radiological Stage	Initial Dx	Final Dx	Mets during therapy	Size (mm)	Rete invasion	TNM stage	Necrosis	Days CTX to orchi	CTX regimen	CTX	BL AFP	Max AFP in FU	Min AFP in FU	Alive June 2022
P_1	39	Seminoma contralateral testis 1995	IIIa	Seminoma	Seminoma	No	13	Yes	pT1	No	40	BEP 3 day	3-day BEP x 3	10	15	10	Yes
P_2	43	COPD, gastric ulcer	I	Seminoma	Seminoma	No	25	Yes	pT1	No	42	CARBO (AUC) GCT	carbo (AUC 7) x 1	11	15	9	Yes
P_3	45	Bilateral microlithiasis	I relapsed to IIa at 7 months	Seminoma	Seminoma	Yes (Stage 2 @ 6–7 months)	20	No	pT1	Yes (focal)	262	CARBO (AUC) GCT	carbo (AUC 7) x 1 + PA XRT	10	12	2	Yes
P_4	65	Undescended testes, Down's Syndrome, chronic lung disease, left gynaecomastia, hypothyroidism, dementia	I	Seminoma	Seminoma	No	50	Yes	pT2	No	35	CARBO (AUC) GCT	carbo (AUC 7) x 1	9	10	7	No
P_5	31	Testis surgery childhood, torsion and bilateral orchidopexy	I	Seminoma	Seminoma	No	30	No	pT1	No	43	CARBO (AUC) GCT	carbo (AUC 7) x 1	9	10	8	Yes
P_6	29	No	I	Seminoma	Seminoma	No	24	Yes	pT2	No	50	CARBO (AUC) GCT	carbo (AUC 7) x 1	8	10	7	Yes
P_7	35	Depression	I	Seminoma	Seminoma	No	40	Yes	pT1	No	35	CARBO (AUC) GCT	carbo (AUC 7) x 1	8	8	7	Yes
P_8	32	No	I	Seminoma	Seminoma	No	60	Yes	pT1	Yes (extensive)	39	CARBO (AUC) GCT	carbo (AUC 7) x 1	8	9	7	Yes

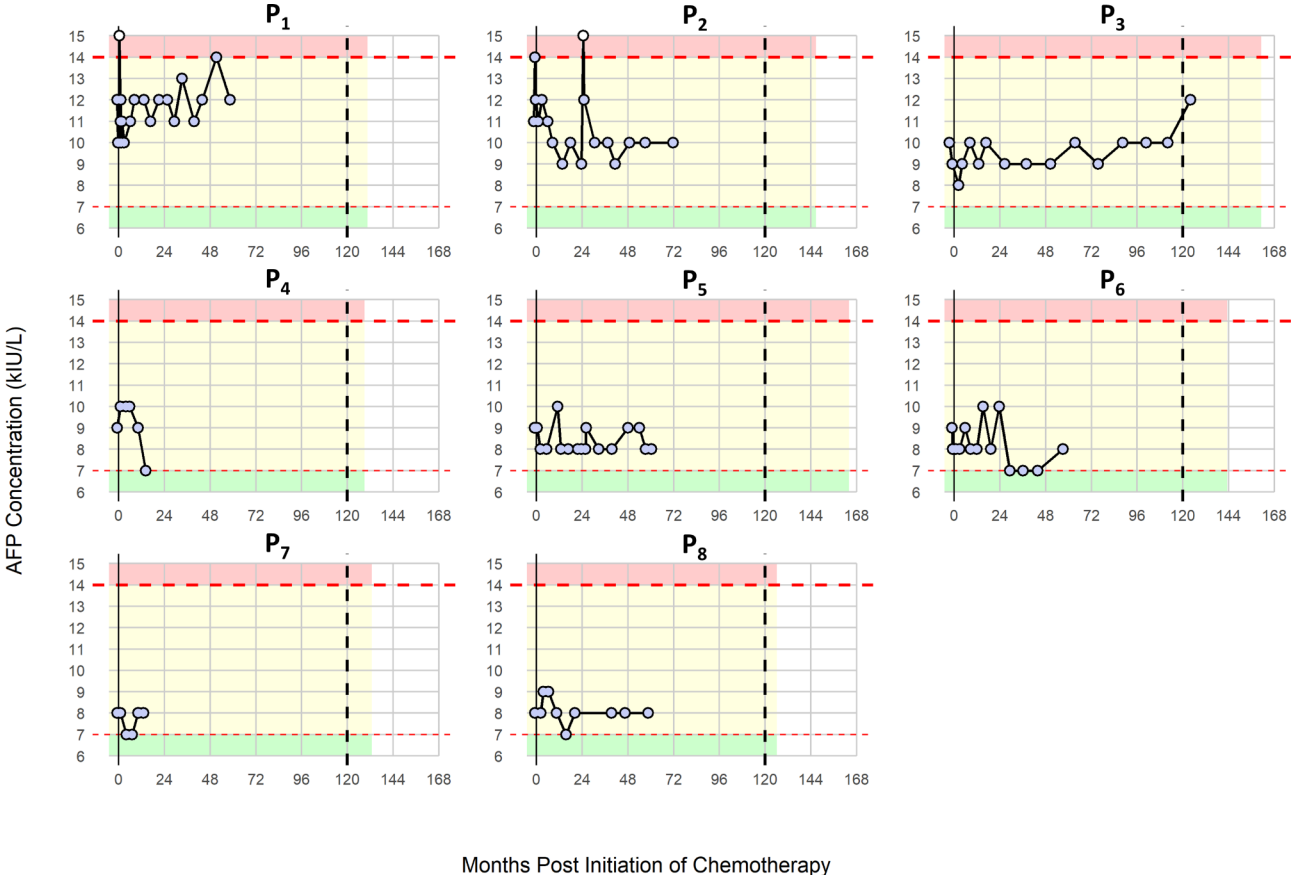

Fig. 1 AFP concentrations over time for eight patients with elevated AFP levels at baseline. AFP timecourses for the eight individual patient cases during the baseline and surveillance periods reviewed at 10 years. The x-axis represents the months post-initiation of surveillance, while the y-axis indicates AFP concentration. AFP concentration ranges below the upper limit of the reference interval ((ULRI) < 7 kIU/L) are in green, the "moderate elevation" range (7–14 kIU/L) is in yellow, while the range twice the ULRI or higher (> 14 kIU/L) is in red. These shaded areas extend only as far as the individual patient follow-up, illustrating the varying surveillance durations for each patient. Horizontal dashed red lines indicate the upper limit of the reference interval (7 kIU/L) and twice the upper limit (14 kIU/L). Vertical solid black lines are drawn at 0 months, marking the start of surveillance, and dashed vertical black lines at 120 months, representing the 10-year follow-up point. Individual data points for AFP measurements are circles. Points filled in grey correspond to AFP concentrations within the green and yellow ranges (≤ 14 kIU/L), while white-filled points indicate AFP concentrations exceeding twice the upper limit of the reference interval (> 14 kIU/L). Each patient's data is presented as a separate plot

thymoma rather than metastatic TC. His disease was retrospectively recategorised as stage 1 disease, and he was included in our cohort. AFP increased significantly in P_1 to a peak of 15 kIU/L on day 14, returning to 11 kIU/L on day 27 and remained moderately elevated until 58.7 mo. P_1 tolerated chemotherapy well, and liver function tests were within normal limits during therapy.

P_2 had a histological diagnosis of TCS with an AFP of 11 kIU/L pre-operatively. AFP increased to 14 kIU/L before the commencement of chemotherapy. At 24.7 mo, a single measurement of 15 kIU/L was taken. This reflected a significant change to his previous measurement. When repeated 14 d later, however, AFP had reduced to 12 kIU/L and remained between 9 kIU/L and 12 kIU/L until the end of the surveillance period at 72.1 mo. No additional investigations were required.

Follow-up of patients with no significant changes in AFP concentration during treatment

In patients with moderate BL elevations of AFP, six ($P_{3\text{-}8}$) remained moderately elevated, with no positive or negative changes in AFP concentration > RCV during follow-up. These patients were still considered to have TCS throughout the follow-up period.

Although P_3 had moderately elevated AFP noted at BL, CT and histology confirmed classical TCS stage 1 without invasion and "no suggestion of non-semanomatous germ cell tumour (NSGCT)". P_3 was placed on intensive imaging and TM surveillance. A CT scan 6–7 mo later indicated stage 2 A metastatic disease, at which point P_3 was commenced on carboplatin chemotherapy and sequential para-aortic radiotherapy. AFP remained moderately elevated at BL, and throughout treatment and follow-up, until the last measured AFP at 124.5 mo. In the remaining patients, no metastases were observed in

these patients in the follow-up period, and one patient, P_4, died. P_4 had a history of undescended testes, Down's Syndrome, chronic lung disease, hypothyroidism and dementia. The cause of death is not recorded on the electronic patient record at LCC but is not thought to be related to his TC.

Biological variability for AFP and frequency of elevated AFP in Seminoma patients

For the seminoma patients included in this study, the CV_i for AFP was 10.3%, higher than the 4.5% quoted in reference databases [23]. The frequency of elevated AFP in the seminoma group was at least 4.1%, compared with 1.6% in the reference population. Thus, elevated AFP was at least 2.6 times more frequent amongst seminoma patients in this study than in the reference population.

Discussion

Patients with mild, stable elevations of AFP

In most subjects with moderate elevations of AFP at BL, AFP remained stable during follow-up, and none relapsed within the study period following treatment for seminoma. Recently, a study discussed "falsely elevated" AFP in patients with TC, who demonstrated moderate, stable elevations, not associated with disease or treatment, during prolonged follow-up [14]. The authors cautioned against interpreting moderate AFP elevations as evidence of embryonal carcinoma or yolk sac tumour and warned against inappropriate interventions. This study confirms, specifically for a TCS cohort, that some patients exhibit stable, moderate AFP elevations of unknown aetiology. However, these elevations were lower than those observed in the abovementioned study [14]. Consistent with previous assertions, this study reinforces that AFP elevations alone should not prompt alterations in diagnosis or chemotherapy but should be interpreted alongside other diagnostic measures.

Patients with significant changes in AFP during chemotherapy in this study

Significant changes in AFP concentration were observed in just two patients during surveillance, although the maximum AFP observed for both men was 15 kIU/L. In neither case could this be correlated to disease status, therapeutic interventions, or any related comorbidity. However, one patient, initially treated for stage 3 disease, underwent a chemotherapy regimen identical to that used for NSGCT, in which AFP elevations are common. In this case, an AFP rise due to tumour lysis of a possible NSGCT component cannot be excluded.

Strengths and deficiencies of this study

Strengths of this study include the fact that patient selection relied upon histological and staging information about patients at diagnosis, offering an unselected patient population.

Patient notes were retrospectively examined, and all study participants are now at least ten years from their initial diagnosis and chemotherapy. One patient died, and two were lost to follow-up, but the remainder completed the initial five years of formal surveillance activity. We, therefore, have robust data for this cohort about their long-term outcomes.

The authors identify the following deficiencies in this study: the study focuses on patients with moderate elevation of AFP at BL and does not consider patients with a change in AFP activity > RCV where the original BL measure was < ULRI. Further, since this is an observational study, there is a lack of uniformity in follow-up data, and the patient record could not be examined for an equal follow-up period in all patients.

Defining "elevated AFP" in seminoma patients

Of importance is the definition of an abnormally elevated AFP. An assay-specific ULRI is used in this study, while other studies have defined higher cut-offs as clinically significant elevations of AFP based on local experience [13–16]. The authors suggest that clinical consideration should be given to all elevations of AFP > ULRI. Within our cohort, the highest level of AFP in patients not requiring a change in management was 15 kIU/L.

Significance of AFP elevations in seminoma

Elevations of AFP in patients with histologically confirmed TCS may suggest several possibilities:

1. TC is classified incorrectly, and a non-seminoma element has been overlooked during the histological examination.
2. Comorbidities such as liver dysfunction, metastases, or tumour lysis syndrome.
3. An alternative AFP-producing tumour elsewhere.
4. Analytical factors, including assay reformulation or interference.
5. Moderate, stable AFP concentrations reflecting biological variability in the healthy population.

Understanding the aetiology of elevated AFP is vital since misinterpretation may lead to significant morbidity in these patients.

This study observed moderate elevations of AFP at BL and during surveillance in a small but significant proportion of men with new diagnoses of TCS. There was no apparent reason for raised AFP in these subjects, such as alcohol abuse, hepatitis, cirrhosis, biliary tract obstruction, and Fanconi anaemia, and there was no GCT relapse in these patients.

A key question is whether the patients with moderate elevations of AFP merely reflect biological variability in a healthy population. Although mild AFP elevations appear stable and independent of disease progress or chemotherapy, frequency in this group is more than three times that expected in the healthy population. Thus, they may not all represent physiological elevations. It is not immediately apparent if there is a mechanism for increased AFP associated with a seminomatous state, and the reasons for AFP elevation in this group remain obscure.

Interestingly, incipient yolk sac tumour (YST) micropopulations have been observed within seminomas. Forkhead box protein A2 (FOXA2) is considered a master regulator of YST formation, driving the reprogramming and differentiation of seminoma cells into YST-like cells through epigenetic mechanisms [31] and involving other transcription factors such as Sex-determining region Y-box 2 (SOX2) and SOX7, PReferentially expressed Antigen in Melanoma (PRAME), and Hepatocyte Nuclear Factor 1β (HNF1β) [32–36]. Although subpopulations of FOXA2-positive cells in pure seminomas are associated with increased tumour aggressiveness, potentially prompting therapeutic adjustment, they are not associated with altered AFP expression relative to seminomas lacking FOXA2 expression [37, 38]. Therefore, while it is striking that the prevalence of AFP elevations in the cohort described is similar to the ~5% prevalence of FOXA2-positive seminomas reported in prior studies [38], it is difficult to ascribe the patterns observed to this mechanism. However, the authors suggest that the role of transcription factors and epigenetics in reprogramming micro populations of AFP-producing seminomas warrants further investigation.

In this study, neither moderated elevations of AFP nor significant changes in AFP, albeit still within the moderately elevated range, led to any inappropriate patient management at this centre. Indeed, the AFP concentrations and changes did not impact the treatment or management of any of the subjects described. However, the risk remains, particularly at less specialist centres, that the AFP concentrations and changes observed in this cohort might confuse and delay appropriate diagnosis, treatments and surveillance of patients with TCS.

Conclusions

In a large comprehensive retrospective study of clinical records in a regional cancer centre, the authors observe moderate and stable elevation of AFP in a significant number of new diagnoses of TCS. In this group, the biological variability appears higher, and elevated AFP is more frequent than in the normal population. The significance of stable AFP elevations remains unclear but does not relate to disease or therapy and did not alter patient management at any stage. However, centres should be vigilant to the phenomenon of AFP elevations in this patient group so as not to alter diagnoses, treatment or follow-up in a clinically inappropriate manner.

Abbreviations

AFP	α-Fetoprotein
AUC	Area Under the Curve
BEP	Bleomycin, Etoposide, and Platinum
BL	Baseline
CT	Computed Tomography
CTX	Chemotherapy
CV	Coefficient of Variation
CV_a	Analytical Coefficient of Variation
CV_i	Intra-individual Biological Variability
D_x	Diagnosis
FOXA2	Forkhead box protein A2
FU	Follow-up
GCT	Germ Cell Tumour
hCG	Human Chorionic Gonadotropin
HNF1β	Hepatocyte Nuclear Factor 1β
Hx	Past Medical History
IQR	Interquartile Range
LCC	Leeds Cancer Centre
Mets	Metastases
mm	Millimetre
mo	Months
NHS	National Health Service
NSGCT	Non-Seminomatous Germ Cell Tumour
PID	Patient Identifier
PRAME	PReferentially expressed Antigen in Melanoma
REC	Research Ethics Committee
RCV	Reference Change Value
SOX2	Sex-determining region Y-box 2
SOX7	Sex-determining region Y-box 7
TC	Testicular Cancer
TCS	Testicular Classical Seminoma
TM	Tumour Marker
TNM	Tumour-Node-Metastases classification
ULRI	Upper Limit of the Reference Interval
UK	United Kingdom
yr	Years
YST	Yolk sac Tumour

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Author contributions

SJC (Seán J. Costelloe): Conceptualised the study, led the data analysis, and wrote the manuscript.JDS (Jennifer D. Spencer): Contributed to data analysis, interpretation of results, and manuscript drafting.KH (Kathryn Humphries): Assisted with data collection, statistical analysis, and manuscript revisions. DS (Daniel Stark): Provided clinical oversight, helped interpret findings, and reviewed the manuscript critically for important intellectual content.ED (Elaine Dunwoodie): Facilitated access to data and contributed to study design and manuscript revisions. All authors read and approved the final manuscript.

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Data availability

The datasets used and analysed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study complied with UK data protection legislation and Caldicott guidelines. All patient records and laboratory results were accessed only by clinicians and scientists directly involved in patient care. Patients were treated according to standard care protocols; no interventions or changes to their care were made due to this study. All data were anonymised prior to analysis by removing direct patient identifiers and assigning unique study identifiers. According to the NHS Health Research Authority online decision tool, a formal review by the NHS Research Ethics Committee (REC) was not required for this study due to its retrospective design and the use of anonymised patient data. The study was approved by the Caldicott Guardian at the Leeds Cancer Centre (LCC).

Consent for publication

Not applicable. This study does not contain any individual person's data in any form (including individual details, images, or videos).

Competing interests

The authors declare no competing interests.

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