sciendo Acta Marisiensis - Seria Medica 2023;69(1):50-54 DOI: 10.2478/amma-2023-0008

RESEARCH ARTICLE

Testosterone deficiency is associated with clinically relevant depression symptoms

Liliana Vartolomei[1*], Sabin Octavian Tătaru[1], Andrei Cotruș[2], Camelia Stanciu[2], Anca Ileana Sin[3]

1. IOSUD, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania
2. Department of Psychology, Dimitrie Cantemir University, Targu Mures, Romania
3. Department of Cell and Molecular Biology, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania

Objective: To investigate the association between testosterone deficiency and depressive and/or anxiety symptoms. **Methods**: A cross-sectional study was conducted at the urology outpatient clinic from Ludus County Hospital. A set of validated questionnaires ((International Prostate Symptoms Score (IPSS), Depression Anxiety and Stress Scale (DASS-21), Zung Self-rating Depression Scale (Zung SDS)) were self-administrated. Inclusion criteria: age > 40 years. Exclusion criteria: any relevant psychiatric, cardiovascular, or cancer comorbidity. Statistical analyzes were performed using the statistical software Statistical Package for Social Sciences (SPSS, version 23, Chicago, IL, USA). **Results**: From the total of 55 participants included in the study, 23 (41.8%) had testosterone deficiency. Most were from the 60-69 years decade, 23 participants (41.8%), and the mean age was 59.3 (SD 9.03) years. Eleven (20%) patients had depressive symptoms according to the depression subscale, of these, 7 had mild symptoms and 4 according to Zung SDS. Testosterone deficiency was associated with an increased DASS-21 global score, p=0.021, and depression score, p=0.047. **Conclusions**: Patients with testosterone deficiency are presenting symptoms of depression. Therefore, these patients need a multi-disciplinary approach that should include a psychological evaluation before making a further management decision.

Keywords: testosterone deficiency, depression, anxiety, stress

Received 25 October 2022 / Accepted 9 February 2023

Introduction

Depression is a common disease worldwide, with a reported incidence of approximately 3.8% of the global population, with this incidence increasing to 5.0% among adults and 5.7% among adults over 60 years of age. Thus, according to data from the World Health Organization (WHO), approximately 280 million people in the world suffer from depression [1].

Depression differs from regular mood swings and short-lived emotional responses to the challenges of everyday life. In particular when it is recurrent and of moderate or severe intensity, depression can become a serious health problem, which influences the individual's functioning at work, at school, and in the family [2]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5), depressive disorders can embrace many faces from a major depressive episode to other unspecified manifestations [3].

Testosterone represents the main male hormone responsible for sexual development and maintenance of secondary sexual characteristics [4]. The mechanism of action involves crossing the cell membrane, binding to specific receptors, and deoxyribonucleic acid (DNA) to facilitate both ribonucleic acid (RNA) and protein synthesis. It is involved among others in the growth of muscles, bone mass, penis, and scrotum [5].

The term late-onset hypogonadism appeared in 2002, defined as a syndrome, characterized by specific symptoms and serum testosterone deficiency (TD) [6]. Men with TD present with loss of libido, dysphoria, fatigue, and/or irritability symptoms [7] that may correlate with depression episodes [8]. A linkage may be because episodes of major depression are increasing with aging [9], while testosterone decreases [10]. Consecutively, a correlation between TD and depressive symptoms might increase with age [11]. The most present depressive symptoms in patients with age-related TD are dysthymia, hopelessness and suicidal thoughts [12,13].

Even so, a correlation between TD and major depression is still under investigation, the current literature indicates a link in men with refractory depression, major depression and/or HIV infection, dysthymia, and/or in elderly (age >60 years) [14]. Refractory depression or treatment resistant depression is considered in case of failure to achieve remission after treatment with one or two antidepressant of same or different classes [15].

Thus, our aim was to investigate the association between testosterone deficiency and depressive and/or anxiety symptoms by conducting a cross-sectional study.

Materials and Methods

A cross-sectional study was performed from 1st January to 31st March 2020. A set of validated questionnaires ((International Prostate Symptoms Score (IPSS), Depression Anxiety and Stress Scale (DASS-21), Zung Self-rating Depression Scale (Zung SDS)) were applied to 55 men, aged between 40 and 75 years, who consecutively presented themselves for a specialist urological consultation at the outpatient clinic from Luduș County Hospital.

* Correspondence to: Liliana Vartolomei
E-mail: liliana.vartolomei17@gmail.com

Participants

Inclusion criteria: age > 40 years. Exclusion criteria: any relevant psychiatric, cardiovascular or cancer comorbidity. The current study was approved by the local Ethical Committee (No. 2441/2019). It was explained to each subject what the applied questionnaires consisted of, how to complete them, the questionnaire set, and the informed consent were handed to each subject. Questionnaires were completed by the participants and clinical data such as serum testosterone and prostate specific antigen (PSA) values were also recorded. The acceptance rate to participate in the study was 91.6 %, 55 participants out of 60 approached.

Data collection

The data completed by the participants were centralized in an Excel database that included age as a continuous variable (coded by decades of age), PSA value (ng/dl), prostate gland volume measured with ultrasound, PSA density (calculated as the ratio PSA/prostate volume), testosterone (ng/dl), testosterone deficiency (TD, coded according to the recommendations of the American Urology Association: testosterone ≤300 ng/dl on two consecutive determinations), followed by the global score of the psychometric questionnaires and their interpretation according to the recommended coding and the answers to each item of these questionnaires. Total scores corresponding to the scales were calculated by summing the ratings for each response according to the rating manuals.

Psychometric tests

DASS-21 [16] was used to determine symptoms of depression, anxiety, and stress. This test can evaluate the severity of behavioral and emotional symptoms that are correlated with depression, anxiety disorder and stress. We used the 21 items test with specific questions for depression: items 3, 5, 10, 13, 16, 17, and 21; anxiety: items 2, 4, 7, 9, 15, 19, and 20; and stress: items 1, 6, 8, 11, 12, 14, and 18. Each of the questions was rated from 0 to 3. The final score was then converted in a Z-value according to age and gender, and according to Z-value patients were assigned to one of four categories (normal, mild, moderate, and severe symptoms) [17].

Zung SDS [18] contains 20 items and was designed based on the specific diagnostic criteria for depression. Participants rate each item using a 4-point Likert scale. The scores of the Zung SDS ranges from 20 to 80 but results are converted to a SDS Index to a 100 points scale.

Statistical analysis

Associations between age, testosterone deficiency with responses to questionnaire items (DASS-21 and Zung SDS) were quantified using the chi^2 test. Differences between continuous variables (DASS and Zung SDS score) according to the variables studied, were analyzed using the student t-test. Statistical significance was defined as a $p < 0.05$. Statistical analyzes were performed using the statistical software Statistical Package for Social Sciences (SPSS, version 23, Chicago, IL, USA).

Results

Patients' characteristics

From the total of 55 participants included in the study, 23 (41.8%) had testosterone deficiency (TD). Most were from the 60-69 age decade, 23 participants (41.8%) (Table 1), and the mean age was 59.3 (SD 9.03) years. The mean prostate volume measured by ultrasound was 28.7 (SD 17.29) cm^3, the mean value of prostate specific antigen was 1.96 ng/dl (SD 1.69), with a mean PSA density of 0.09 (SD 0.15). Regarding lower urinary tract symptoms, 27 participants reported mild symptoms, 20 moderate symptoms and 8 patients - severe symptoms (Table 1).

Depression, anxiety, and stress according to DASS-21 and Zung SDS

The median score at DASS-21 was 9 (interval 0-35) and at Zung SDS was 37.5 (interval 25-56.25). Eleven (20%) patients had depressive symptoms according to the depression subscale of the DASS-21, of these, 7 had mild symptoms. Ten (18.2%) patients had anxiety symptoms according to the anxiety subscale of the DASS-21, with 3 that had severe symptoms, all these 3 patients had also moderate or severe depression and stress symptoms, of which 2 patients (66%) were with TD. Another 6 patients (10.9%) had symptoms of stress according to the stress subscale of DASS-21. According to Zung SDS questionnaire, 4 (7.3%) patients had a score between 50 and 59, which means with mild depressive symptoms (Table 2).

Testosterone deficiency and depression

A statistically significant association was identified between DASS-21 global score and TD, p=0.021 and DASS Depression and testosterone deficiency, p=0.047 (Table 3). The item analysis demonstrated a statistically significant association between TD and agitation: 60.9% vs.

Table 1. Patients' characteristics

Characteristic		Patients	Percentage
Age (years)	40-49	9	16.4
	50-59	17	30.9
	60-69	23	41.8
	70-75	6	10.9
Testosterone deficiency	<300 ng/dl	23	41.8
International Prostate Symptoms Score	1-7	27	49.1
	8-19	20	36.4
	20-35	8	14.5

Table 2. DASS-21 and Zung SDS interpretation

Questionnaire subscale	Interpretation	Patients	Percentage
DASS-21 depression	No symptoms	44	80
	Mild symptoms	7	12.7
	Moderate symptoms	2	3.6
	Severe symptoms	2	3.6
DASS-21 anxiety	No symptoms	45	81.8
	Mild symptoms	3	5.5
	Moderate symptoms	4	7.3
	Severe symptoms	3	5.5
DASS-21 stress	No symptoms	49	89.1
	Mild symptoms	3	5.5
	Moderate symptoms	3	5.5
Zung SDS	No symptoms	51	92.7
	Moderate symptoms	4	7.3

Table 3. Association of testosterone deficiency (TD) with depression, anxiety and stress symptoms according to DASS-21

TD		DASS-21	DASS-21 Depression	DASS -21 Anxiety	DASS -21 Stress
no	Mean	8.31	2.97	2.63	2.72
	Std. Deviation	6.029	2.192	2.511	2.275
	Median	8.00	3.00	2.00	3.00
	Minimum	0	0	0	0
	Maximum	30	10	11	9
	Patients	32	32	32	32
yes	Mean	12.83	4.48	4.13	4.22
	Std. Deviation	8.721	2.952	3.415	2.969
	Median	11.00	4.00	4.00	3.00
	Minimum	1	1	0	0
	Maximum	35	12	13	12
	Patients	23	23	23	23
total	Mean	10.20	3.60	3.25	3.35
	Std. Deviation	7.543	2.622	2.989	2.668
	Median	9.00	3.00	2.00	3.00
	Minimum	0	0	0	0
	Maximum	35	12	13	12
	Patients	55	55	55	55
P value		0.021	0.047	0.073	0.060

21.9% (p=0.012), and lower self-esteem: 47.8% vs. 12.5% (p=0.014).

Discussion

In our study, patients with testosterone deficiency were more likely to have higher DASS-21 scores (overall for depression, anxiety, and stress symptoms) and a statistically significant association was found also with depression symptoms scores. When present, severe anxiety symptoms are associated with moderate and severe depression and stress symptoms and with TD. Similarly, three studies identified an increased prevalence of depression among men with TD compared with those without TD. Using an 11-point reference value of the Beck Depression Inventory (BDI) scale, Rotter et al. [19] reported a prevalence of 30.9% vs. 26.4%, and Boeri et al. [20] a prevalence of 52.4% vs. 23.8%. In contrast, Jankovska et al. used a reference value of 16 on the BDI scale to define depressive symptoms and identified that in the group of patients with depressive symptoms, 31% also had testosterone deficiency, compared to 12% in the group without depressive symptoms [21].

Furthermore, other studies have identified that patients with depressive symptoms have a lower average testosterone value than those without depressive symptoms [22,23]. Likewise, 3 other studies have identified a correlation between testosterone levels and severity of depression [24–26]. Kong et al. instead demonstrated a positive correlation between Aging Males Symptoms (AMS) and BDI scores, r=0.5, p<0.01 [27]. Contrary, a study that included 3413 men from the Norwegian city of Tromsø did not identify a correlation between testosterone levels and mental disorder defined by a score > 1.85 on the Hopkins Symptom Checklist-10 scale [28]. This may be due to general population characteristics in this specific geographical area [29].

We found that one out of five patients investigated is presenting with depressive symptoms according to DASS-21 depression subscale. On the other hand, when using Zung SDS scale less than 10% presented clinically relevant depression symptoms. However, when using a lower cut-off the percentage may increase [30]. Taking together, DASS-21 can be used as a screening tool in adult males as was previous proved in other populations [31–33], and this must be doubled by another specific psychometric test [34] and clinical interview to conclude if the patients are meeting the DSM-V criteria [3] and if they are needing any kind of intervention or pharmacological treatment [35].

As current literature advocate that depression represents a combination of genetic, biological, environmental, and psychological factors, everything must be taking into account [36]. Furthermore, particular in elderly may co-exist with other serious medical conditions, such as cancer, cardio-vascular diseases, diabetes, or Parkinson's disease, with a reported incidence of up to 28% among the elderly with such comorbidities, according to the latest meta-analysis. In young men, it can be associated with erectile dysfunction [37]. These comorbidities are often exacerbating in the presence of depression and frequently drugs that are taken for these ailments can produce side effects that favor depression manifestation.

In our cohort more than 40% of patients had TD, which represent a quite large number when compared to the current literature, which establish a prevalence up to 10% in western countries [38], similar in Asian cohorts, in a Indian cohort 22% [39] or 5.8% in a population from Korea [40]. Similar findings were reported by the Hypogonadism In Men study, which reported a prevalence of TD of 38.7% [41], therefore the prevalence might be heterogeneous among different populations.

Lower baseline levels of testosterone were also shown to be associated with a longer durations of positive COVID-19 testing and thus viral clearance in males hospitalized for COVID-19 infection [42]. In case of prostate cancer (PCa) diagnosis, lower baseline testosterone levels were associated with unfavorable prognosis in patients undergoing active surveillance for low risk PCa [43] or in case of those undergoing radical prostatectomy [44].

This study should be viewed considering several limitations. Firstly, there is a subject selection bias. The patients do not represent a randomly selected group to represent the general characteristics of adult men over 40 years of age. Secondly, there is a limitation related to the number of participants that were included in the study. Thirdly, there is a limitation related to the methodology, techniques and questionnaires used. After designing the study, we found that it would have been interesting to apply other questionnaires such as the Hospital Anxiety and Depression Scale (HADS), which could have helped to double the results in terms of anxiety, as was shown in a different setting and population that a lower cut point for anxiety in the DASS-21 scale is required to equate prevalence according to HADS [45], contrary in another study a statistically significant correlation was reported, with a Spearman's rank correlation value of 0.83 [46]. Despite this limitations, the results open new directions of research in relation to the need for a multi-disciplinary approach to the problem of patients with TD, which of course also includes a psychological assessment of the patient. To validate and generalize the results obtained in the present study, future studies should also focus on the effects of combined, psychological, and pharmacological therapies (eg. different forms of testosterone replacement therapy) on these specific symptoms.

Conclusion

Patients with testosterone deficiency are presenting symptoms of depression. Consequently, these patients need a multi-disciplinary approach that should include a psychological evaluation prior to any decision making regarding further management.

Authors' contribution

LV - Study design, data analysis, critical revision and editing of manuscript, final approval for publication; SOT - Study design, research implementation, drafting of manuscript, data collection, final approval for publication; AC - Study design, study validation and supervision, critical review of manuscript, final approval for publication; CS - Study design, data analysis, critical review of manuscript, final approval for publication; AIS - Study design, data analysis, critical review of manuscript, final approval for publication;

Conflicts of interest

None to declare

References

1. Depression. (WHO). Retrieved May 26, 2022, from https://www.who.int/news-room/fact-sheets/detail/depression.
2. Dinesh AA, Helena Pagani Soares Pinto S, Brunckhorst O, et al. Anxiety, depression and urological cancer outcomes: A systematic review. Urol Oncol. 2021;39:816–828.
3. Diagnostic and Statistical Manual of Mental Disorders: DSM 5. 5th ed., American Psychiatric Association, 2013.
4. Akerman J, Kovac JR, Lipshultz LI. Testosterone therapy improves well being and psychological health. Curr Opin Urol. 2017;27:519–524.
5. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and Management of Testosterone Deficiency: AUA Guideline. J Urol. 2018;200:423–432.
6. Nieschlag E. Late-onset hypogonadism: a concept comes of age. Andrology. 2020;8:1506–1511.
7. Mani SB, Clavijo RI. Medical Treatment of Hypogonadism in Men. Urol Clin North Am. 2022;49:197–207.
8. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Association of sex hormones with sexual function, vitality, and physical function of symptomatic older men with low testosterone levels at baseline in the testosterone trials. J Clin Endocrinol Metab. 2015;100:1146–1155.
9. Han LKM, Dinga R, Hahn T, et al. Brain aging in major depressive disorder: results from the ENIGMA major depressive disorder working group. Mol Psychiatry. 2021;26:5124–5139.
10. Snyder PJ. Decreasing testosterone with increasing age: more factors, more questions. J Clin Endocrinol Metab. 2008;93:2477–2478.
11. Amiaz R, Seidman SN. Testosterone and depression in men. Curr Opin Endocrinol Diabetes Obes. 2008;15:278–283.
12. Zitzmann M. Testosterone, mood, behaviour and quality of life. Andrology. 2020;8:1598–1605.
13. Barone B, Napolitano L, Abate M, et al. The Role of Testosterone in the Elderly: What Do We Know? Int J Mol Sci. 2022;23:3535.
14. Vartolomei MD, Kimura S, Vartolomei L, et al. Systematic Review of the Impact of Testosterone Replacement Therapy on Depression in Patients with Late-onset Testosterone Deficiency. Eur Urol Focus. 2020;6:170–177.
15. Nuñez NA, Joseph B, Pahwa M, et al. Augmentation strategies for treatment resistant major depression: A systematic review and network meta-analysis. J Affect Disord. 2022;302:385–400.
16. Lovibond, S. H., & Lovibond, P. F. (1993). Manual for the Depression Anxiety Stress Scales (DASS). Psychology Foundation Monograph.
17. DASS: manual pentru scalele de depresie,anxietate şi stress: DASS 21-R: adaptarea şi standardizarea DASS pe populaţia din România / S.H Lovibond, P.F. Lovibond; adaptare: Perţe Adela, Monica Albu. Cluj-Napoca: Editura ASCR, 2011.
18. Zung WW. A SELF-RATING DEPRESSION SCALE. Arch Gen Psychiatry. 1965;12:63–70.

19. Rotter I, Wiatrak A, Rył A, et al. The Relationship between Selected Bioelements and Depressiveness Associated with Testosterone Deficiency Syndrome in Aging Men. Med Kaunas Lith. 2020;56:E125.
20. Boeri L, Capogrosso P, Ventimiglia E, et al. Does Calculated Free Testosterone Overcome Total Testosterone in Protecting From Sexual Symptom Impairment? Findings of a Cross-Sectional Study. J Sex Med. 2017;14:1549–1557.
21. Jankowska EA, Drohomirecka A, Ponikowska B, et al. Deficiencies in circulating testosterone and dehydroepiandrosterone sulphate, and depression in men with systolic chronic heart failure. Eur J Heart Fail. 2010;12:966–973.
22. Monteagudo PT, Falcão AA, Verreschi ITN, et al. The imbalance of sex-hormones related to depressive symptoms in obese men. Aging Male Off J Int Soc Study Aging Male. 2016;19:20–26.
23. Peng R, Li Y. Associations Between Tenascin-C and Testosterone Deficiency in Men with Major Depressive Disorder: A Cross-Sectional Retrospective Study. J Inflamm Res. 2021;14:897–905.
24. Barrett-Connor E, Von Mühlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. J Clin Endocrinol Metab. 1999;84:573–577.
25. Delhez M, Hansenne M, Legros J-J. [Testosterone and depression in men aged over 50 years. Andropause and psychopathology: minimal systemic work-up]. Ann Endocrinol. 2003;64:162–169.
26. Kratzik CW, Schatzl G, Lackner JE, et al. Mood changes, body mass index and bioavailable testosterone in healthy men: results of the Androx Vienna Municipality Study. BJU Int. 2007;100:614–618.
27. Kong X -b, Guan H -t, Li H -g, et al. The ageing males' symptoms scale for Chinese men: reliability,validation and applicability of the Chinese version. Andrology. 2014;2:856–861.
28. Berglund LH, Prytz HS, Perski A, et al. Testosterone levels and psychological health status in men from a general population: the Tromsø study. Aging Male Off J Int Soc Study Aging Male. 2011;14:37–41.
29. Jaswal V, Kishore K, Muniraju M, et al. Understanding the determinants of happiness through Gallup World Poll. J Fam Med Prim Care. 2020;9:4826–4832.
30. Jokelainen J, Timonen M, Keinänen-Kiukaanniemi S, et al. Validation of the Zung self-rating depression scale (SDS) in older adults. Scand J Prim Health Care. 2019;37:353–357.
31. Shah SMA, Mohammad D, Qureshi MFH, et al. Prevalence, Psychological Responses and Associated Correlates of Depression, Anxiety and Stress in a Global Population, During the Coronavirus Disease (COVID-19) Pandemic. Community Ment Health J. 2021;57:101–110.
32. Moya E, Larson LM, Stewart RC, et al. Reliability and validity of depression anxiety stress scale (DASS)-21 in screening for common mental disorders among postpartum women in Malawi. BMC Psychiatry. 2022;22:352.
33. Nilges P, Essau C. [Depression, anxiety and stress scales: DASS--A screening procedure not only for pain patients]. Schmerz Berl Ger. 2015;29:649–657.
34. Mitchell C, Dwyer R, Hagan T, et al. Impact of the QOF and the NICE guideline in the diagnosis and management of depression: a qualitative study. Br J Gen Pract J R Coll Gen Pract. 2011;61:e279-289.
35. Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32:1605–1619.
36. McCarron RM, Shapiro B, Rawles J, et al. Depression. Ann Intern Med. 2021;174:ITC65–ITC80.
37. Manalo TA, Biermann HD, Patil DH, et al. The Temporal Association of Depression and Anxiety in Young Men With Erectile Dysfunction. J Sex Med. 2022;19:201–206.
38. Wang C, Nieschlag E, Swerdloff RS, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. Aging Male Off J Int Soc Study Aging Male. 2009;12:5–12.
39. Aggarwal V, Menon AS, Verma V. Prevalence of Testosterone Deficiency in Elderly Male and its Association with Frailty and Mobility at a Tertiary Care Centre. Indian J Endocrinol Metab. 2021;25:337–341.
40. Park H-M, Kim H, Lee HS, et al. Inverse association between serum bilirubin level and testosterone deficiency in middle-aged and older men. Sci Rep. 2021;11:8026.
41. Mulligan T, Frick MF, Zuraw QC, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract. 2006;60:762–769.
42. Salciccia S, Eisenberg ML, Maggi M, et al. Modeling the Contribution of Male Testosterone Levels to the Duration of Positive COVID Testing among Hospitalized Male COVID-19 Patients. Diagn Basel Switz. 2021;11:581.
43. Ferro M, Lucarelli G, Bruzzese D, et al. Low serum total testosterone level as a predictor of upstaging and upgrading in low-risk prostate cancer patients meeting the inclusion criteria for active surveillance. Oncotarget. 2017;8:18424–18434.
44. Ferro M, Lucarelli G, de Cobelli O, et al. Circulating preoperative testosterone level predicts unfavourable disease at radical prostatectomy in men with International Society of Urological Pathology Grade Group 1 prostate cancer diagnosed with systematic biopsies. World J Urol. 2021;39:1861–1867.
45. Covic T, Cumming SR, Pallant JF, et al. Depression and anxiety in patients with rheumatoid arthritis: prevalence rates based on a comparison of the Depression, Anxiety and Stress Scale (DASS) and the hospital, Anxiety and Depression Scale (HADS). BMC Psychiatry. 2012;12:6.
46. Kumar K, Kumar S, Mehrotra D, et al. Reliability and psychometric validity of Hindi version of Depression, Anxiety and Stress Scale-21 (DASS-21) for Hindi speaking Head Neck Cancer and Oral Potentially Malignant Disorders Patients. J Cancer Res Ther. 2019;15:653–658.