A Study of Biochemical Markers in Uterine Cancer Diagnosis with Radiotherpay Treatment In Iraq

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Abstract

Background: Uterine cancer is a prevalent gynecological malignancy, with rising incidence rates globally. Early detection and effective treatment are essential for improving patient outcomes. Biochemical markers play a crucial role in diagnosing and monitoring uterine cancer, yet their comprehensive evaluation remains limited. Methods: This study aimed to assess various biochemical markers in the serum of uterine cancer patients compared to healthy individuals. Serum samples from 30 uterine cancer patients and 40 healthy females were analyzed for urea, creatinine, lactate dehydrogenase (LDH) activity, antioxidants (vitamin C and vitamin E), peroxynitrite, and trace elements (calcium and zinc). Results: The study revealed a significant decrease in urea and creatinine levels in serum of uterine cancer patients compared to healthy individuals ($p \leq 0.05$). During radiotherapy, blood urea nitrogen (BUN) exceeded the normal range (7-20 mg/dl), averaging 25.44 ± 9.87 mg/dl before treatment initiation, with no significant decrease during therapy. Serum creatinine levels remained within the normal range. Additionally, a significant reduction in serum vitamin C and vitamin E levels was observed in uterine cancer patients compared to healthy individuals ($p \leq 0.05$). Moreover, there was a significant increase in peroxynitrite and lactate dehydrogenase (LDH) activity, along with a rise in serum calcium levels, and a significant decrease in serum zinc levels among uterine cancer patients ($p \leq 0.05$). Conclusion: The findings highlight the significance of assessing multiple biochemical markers in uterine cancer diagnosis and monitoring. Elevated LDH, peroxynitrite, and calcium levels, along with reduced vitamin C, vitamin E, and zinc levels, may serve as valuable diagnostic markers for uterine cancer.

Keywords: Radiotherapy; Biochemical parameters; Uterine Cancer, Diagnosis, Risk Factors, Treatment

Significance | Effect and investigation of radiotherapy of clinical biomarkers in Uterine Cancer patients.

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Introduction

Uterine cancer is the most prevalent gynecological tumor in affluent countries (Schmeler, K et al., 2005). Diagnosis typically occurs at an average age of 61 years, with a notable subset affecting women under fifty (Schmeler, K et al., 2005). Over the past decade, there has been a noticeable global increase in diagnoses, particularly pronounced in Europe and North America (Siegel, R. L et al., 2019; Clarke M.A, 2018). This rise may be attributed to a simultaneous increase in various risk factors, including obesity, metabolic syndrome, sedentary lifestyle, and prolonged utilization of hormone replacement therapy.

The primary cause of uterine cancer cell development in the endometrium is attributed to unopposed estrogen exposure, particularly in the absence of progesterone. This predominantly affects type I malignancies, constituting 80% of uterine carcinoma cases, characterized by low-grade endometrioid histology and

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typically showing early detection and favorable outcomes (Clarke, M. A., 2018; Boeckstaens, S., 2020). Conversely, type II malignancies, representing 20% of cases, have distinct histopathological characteristics, comprising high-grade endometrioid and non-endometrioid tumors, with a negative prognosis independent of estrogen (Boeckstaens, S., 2020; Bokhman, J. V., 1983). Uterine malignancies constitute around 90% of uterine neoplasms, with uterine sarcomas originating from myometrium or endometrial connective tissues accounting for less than 10% of uterine corpus cancers (Boeckstaens, S., 2020; Bokhman, J. V., 1983). Insufficient empirical support exists regarding potential risk factors associated with long-term Tamoxifen usage and pelvic irradiation history, impacting patient prognosis due to aggressive behavior (Bokhman, J. V., 1983; Felix, A. S., 2010).

Despite the positive prognosis of endometrial cancer, over 11,000 women succumb to the disease annually, primarily due to patients presenting with illness beyond the uterus upon initial diagnosis. While stage III and IV cases represent only 7% and 9% of total diagnoses, respectively, the 5-year survival rates vary from 47% to 58% for stage III tumors and 15-17% for stage IV neoplasms. Enhancing therapy alternatives for these women is imperative (Pozzar et al., 2022). Various factors influence the prognosis of individuals with stage III uterine cancer (Abu-Rustum, N. R et al., 2011).

The presence of abnormal bleeding is a key sign in various forms of uterine cancer, yet its accuracy is limited, with numerous benign conditions manifesting similarly (Boggess, J. F., 2020; Chen, L. M., Yang, 2022). Obesity and advanced age are significant risk factors for postmenopausal women predisposed to uterine cancer (Seebacher, V., 2009; Smith, R. A., 2001). However, alternative potential indicators such as abdominal pain, vaginal secretion, pelvic pressure, and urinary symptoms have not received sufficient emphasis, and knowledge about their significance remains inadequate (Kimura, T et al., 2004, Mahfoudh et al. 2017). Our objective is to gather existing knowledge to identify potential predictors for future risk prediction models, necessitating a thorough examination of various presenting signs and indications (Siegel et al., 2019).

Materials and methods

Study Design

For the investigation of biochemical parameters, 30 blood samples were procured from female patients diagnosed with uterine cancer at the National Oncology Teaching Hospital in Najaf city, aged between 30 and 64 years. Additionally, 40 blood samples were gathered from healthy women in the same age group without any other diseases. The samples were collected in sterile, desiccated tubes and incubated in a water bath at 37°C for 15 minutes. Subsequently, the coagulated portion was separated by centrifugation at 3000 revolutions per minute for 15 minutes, yielding serum that was promptly stored at -20°C.

This research was conducted following the principles set out in the Helsinki Declaration. KUFA UNIVERSITRY ethics board reviewed and approved the study (HK 1052) AT DATE 22/9/2023. Everyone participating in the study gave their consent after being fully informed about the research. Confidentiality was maintained throughout the entire research process.

Determination of Biochemical Parameters

The urea activity was quantified using the Kit method, specifically the version developed by the French Biolabo firm. This enzymatic approach, based on the Talke and Schubert reaction as established by Tiffany et al., correlates urea concentration with absorbance changes at 340 nm over time (Prati, D et al., 2002). The reaction scheme is shown in Scheme 1.

Measurement of s.creatinine activity was conducted using a kit provided by the French Biolabo firm. Initially, endogenous creatine was enzymatically hydrolyzed by a combination of creatinase and sarcosine oxidase, resulting in hydrogen peroxide formation. Catalase was then used to eliminate the hydrogen peroxide. Subsequent reactions involved the introduction of creatinase and 4-aminoantipyrin (4-AA) after catalyst inhibition by salt azide. Creatine produced by creatininase was degraded by both creatinase and sarcosine oxidase, forming hydrogen peroxide. The recently generated hydrogen peroxide was quantified by a linked reaction facilitated by peroxides, utilizing N-ethyl-n-sulphopropyl-m toluidine (TOPS)/4-AA as the chromogen.

LDH analysis was performed using the fortress kit (United Uk), measuring the rate of absorbance change at 340 nm produced by reduction (Tietz, 1976).

The spectrophotometer was employed to measure the levels of serum vitamin C and vitamin E. Vitamin C determination utilized a procedure involving 2,4-dinitrophenylhydrazine (DNPH) as described by Stanley (ST,O. 1979). Assessment of vitamin E in serum was conducted through the Emmerie-Engle Reaction, based on oxidation-reduction reaction principles (Varley, H. 1960).

The peroxynitrite (ONOO-) assay was performed using the Revised approach based on the findings reaction (Vanuffelen et al., 1998). This method relies on peroxynitrite's ability to transform phenol into nitrophenol, measured precisely using a spectrophotometer.

Atomic absorption spectrophotometry methodology, conducted in the research lab of the Faculty of Pharmacy, was employed to measure serum trace element concentrations (Ca++ and Zn++) (Willard et al., 1974).

Statistical Analysis

The statistical analysis of the results was conducted using a T-test at a significance level of $p \leq 0.05$ for comparing the patient group with

the control group. The biochemical parameter values were described using the mean and the standard error.

Results

The study revealed a statistically significant reduction ($p \leq 0.05$) in urea and creatinine concentrations in the serum of fetuses with uterine cancer compared to those without the disease. Throughout radiotherapy, blood urea nitrogen (BUN) levels exceeded the normal range, averaging 25.44 ± 9.87 mg/dl before treatment initiation, with no significant decrease observed during therapy. Serum creatinine levels remained within the normal reference range (0.6-1.1 mg/dl) throughout the various stages of radiation. Despite the elevated BUN levels, waste metabolite concentrations primarily fluctuated within the normal range. Serum vitamin C and vitamin E levels were significantly reduced in females diagnosed with uterine cancer compared to healthy individuals ($p \leq 0.05$), suggesting potential implications for oxidative stress and cellular damage. Peroxynitrite levels were significantly elevated in uterine cancer patients, potentially attributed to an overabundance of superoxide ions generated through nitric oxide interaction. Lactate dehydrogenase (LDH) activity was significantly elevated in uterine cancer patients compared to healthy counterparts ($p \geq 0.05$), indicating cellular damage or destruction, consistent with previous findings in cervical cancer patients. Serum calcium levels exhibited a statistically significant rise in females with uterine cancer compared to healthy females ($p \geq 0.05$), suggesting potential implications for DNA damage and mutagenesis. Conversely, serum zinc levels demonstrated a substantial decrease in females diagnosed with uterine cancer compared to those without the condition, consistent with findings in cervical cancer patients, possibly indicative of cancer cell utilization for growth and membrane stability. These results underscore the intricate biochemical alterations associated with uterine cancer, emphasizing the need for further investigation into their diagnostic and therapeutic implications.

Discussion

The biochemical characteristics of uterine cancer patients are summarized in Table 1. The findings revealed a statistically significant reduction ($p \leq 0.05$) in the concentrations of Urea and Creatinine in the serum of patients with uterine cancer compared to those without the disease. Throughout the course of radiotherapy treatment, biochemical parameters were assessed from course 1 to course 5. Glomerular filtration rate was approximated by blood urea nitrogen (BUN), which exceeded the usual range (7-20 mg/dl) during radiation courses. The study determined that the average BUN level before the initiation of radiation treatment was 25.44 ±9.87. However, a non-significant decrease in BUN levels was observed during radiotherapy treatment (Figure 1, Figure 3). The average serum creatinine levels for patients undergoing radiation for uterine cancer fell within the normal reference range of 0.6-1.1 mg/dl. Prior to the initiation of radiation, the average serum creatinine level was recorded as 0.68±0.39mg/dl. No noticeable changes in creatinine levels were observed during the various stages of radiation (Figure 2, 4).

Blood urea nitrogen (BUN) serves as a highly responsive marker for the presence of renal disorders. In the current investigation, it was observed that the BUN level exceeded the established normal reference range, which differs from findings published in previous investigations (Devi, L et al., 2015). However, the levels of waste metabolites exhibited minor increases and declines, primarily falling within the confines of the normal range. Interestingly, the concentration of urea (BUN) in patients remained within the normal range. On the other hand, the serum creatinine level is regarded as a more sensitive indicator of renal function compared to BUN. Renal dysfunction is the sole factor contributing to increased levels of serum creatinine (s-creatinine). Unlike previous investigations (Devi, L et al., 2015), this study did not find any statistically significant correlation between s-creatinine levels and different courses of radiation. Nevertheless, the elevated s-creatinine level was reported to fall within the range of 1.0 to 2.0 mg/dl.

The findings presented in Table 2 indicate a statistically significant reduction in the serum vitamin C levels among females diagnosed with uterine cancer ($p \leq 0.05$) compared to females without the disease. Interestingly, a similar reduction in vitamin C levels was observed in individuals diagnosed with cervical cancer (Manju et al., 2002). This decline in vitamin C levels may be attributed to its antioxidant properties, as it is utilized to mitigate tissue damage and eliminate free radicals. Vitamin C directly interacts with reactive oxygen species ($O_2^{\bullet}$ and $OH^{\bullet}$) and facilitates the conversion of tocopherol radicals, arising from lipid peroxidation, into vitamin E. Consequently, vitamin C, along with vitamin E, plays a crucial role in safeguarding cells against damage (Head, K. A, 1998; Niki, 1991; Stahl and Sies, 1997).

The results presented in Table 2 demonstrate a statistically significant reduction in serum vitamin E levels among females with uterine cancer ($p \leq 0.05$) compared to those without the disease. This finding is consistent with previous studies on cervical cancer, which also reported decreased vitamin E levels in affected individuals (Manju et al., 2002; Bhuvarahamurthy et al., 1996). The potential decline in vitamin E levels in uterine cancer patients may be attributed to its ability to scavenge lipid peroxides and mitigate cellular damage caused by free radicals (Manju et al., 2002). Vitamin E serves as the primary antioxidant in cell membranes, protecting them against lipid peroxidation and oxidative damage, particularly induced by polyunsaturated fatty acids (Thomas et al., 2000). Studies suggest that consuming vitamins such as vitamin C and E,

either through dietary sources or supplements, may reduce the risk of developing endometrial cancer (Bandera et al., 2009).

The elevation of peroxynitrite levels, specifically nitric oxide (NO)

Table 1: Values of biochemical parameters in females of uterine cancer and healthy females. *Significant differences at P≤0.05

Parameters	Patients (n=)Mean±SD	Control(n=)Mean±SD
Age (Yrs)	40.83± 9.47*	36.67± 11.71
BMI(kg/m2	28.56± 6.45*	24.30± 2.74
S.urea (mg/dl)	25.44 ±9.87*	26.87±7.48
S.creatinine (mg/dl)	0.68±0.39*	0.82±0.19

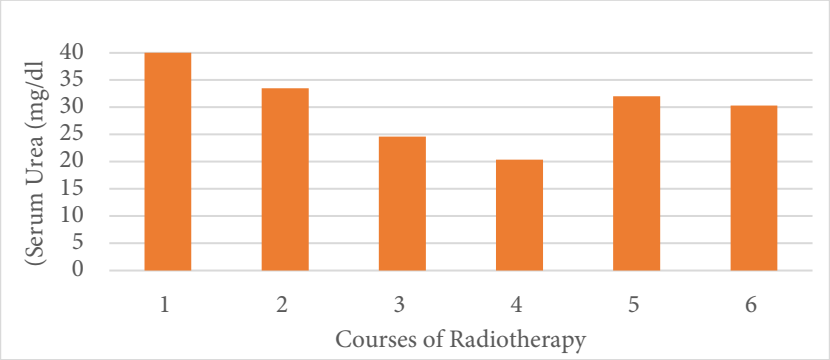

Figure 1. Variations of blood urea count of cancer patients during six courses of radiotherapy.

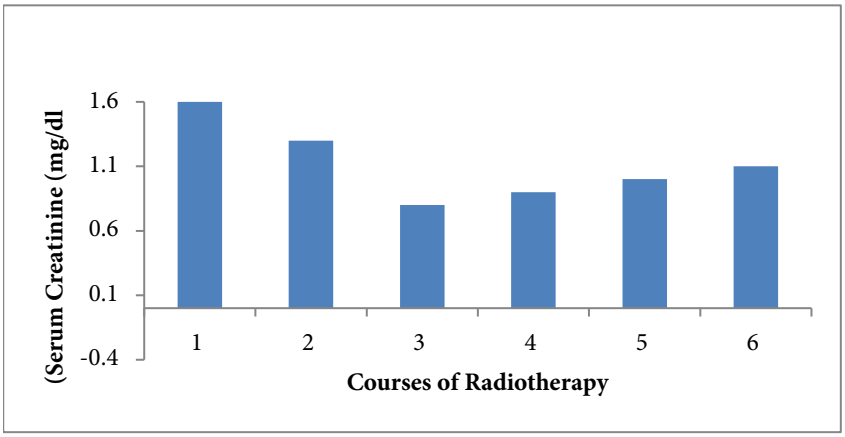

Figure 2. Variations of blood creatinine count of cancer patients during six courses of radiotherapy

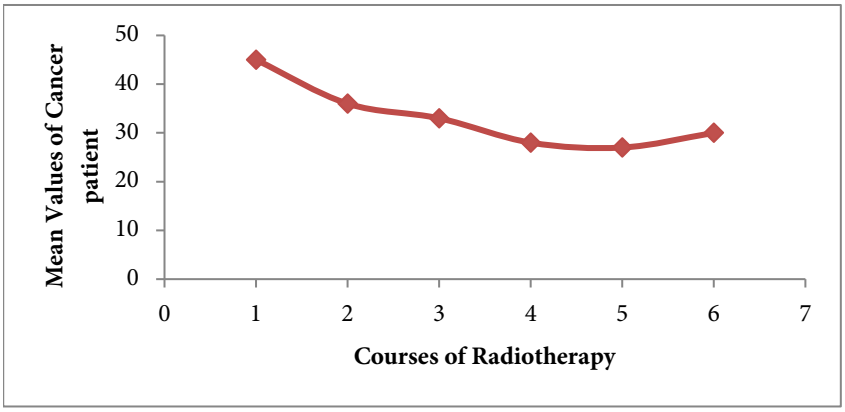

Figure 3. Distribution of serum Urea level in cancer patients during six courses of Radiotherapy

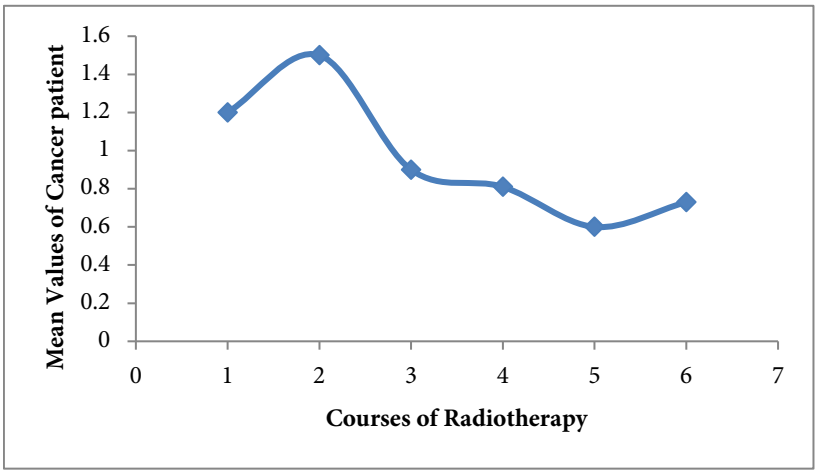

Figure 4. Distribution of serum Creatinine level in cancer patients during six courses of Radiotherapy

Table 2. The comparison of serum biochemical parameters between Patients and Control group(p≤0.05). *Significant differences at P≤0.05

Biochemical parameters	Uterine cancer females (n=)Mean±SD	Control(n=)Mean±SD
Vitamin C (µmol/ L)	24.46 ± 6.18*	39.84 ±8.53
Vitamin E (µmol / L)	12.32 ±2.32*	18.33± 2.22
Peroxynitrite (µmol /L)	97.28± 11.19*	72.66± 12.05
Calcium (µmol /L)	8.83± 0.96*	8. 88 ± 0.62
Zinc (µmol / L)	12.25± 1.67*	15.87± 2.44
Lactate dehydrogenase (U/L)	249.11± 39.38*	155.03± 17.98

and superoxide (O2.-), has been noted to potentially occur in malignancies within living organisms (Cobbs et al., 2003). The findings presented in Table 1 demonstrate a statistically significant increase in peroxynitrite levels in the serum of females diagnosed with uterine cancer compared to those without the disease. This rise in peroxynitrite levels may be attributed to an excess of O2.- ions generated by the interaction between NO and O2.- ions (Cobbs et al., 2003).

Lactate Dehydrogenase (LDH) is an enzyme present in various bodily tissues and is selectively synthesized and retained by cancer cells, aiding in tumor proliferation. Its release into the bloodstream occurs due to cellular damage or destruction, leading to changes in enzyme activity (Rijke and Trienekens, 1985). The results in Table 1 reveal a statistically significant elevation ($p \geq 0.05$) in LDH activity in the serum of females diagnosed with uterine cancer compared to healthy individuals. This finding aligns with previous studies (Subramanian et al., 2009; Kumar et al., 1988) that also reported increased LDH activity in individuals with cervical cancer. These alterations in LDH activity serve as valuable tumor markers for diagnosis, monitoring disease progression, and assessing malignancy levels. The observed increase in LDH activity is attributed to genomic alterations during malignant transformation, primarily driven by heightened lactic acid production by tumor cells through glycoprotein degradation (Subramanian et al., 2009).

The serum calcium levels in females diagnosed with uterine cancer show a statistically significant increase ($p \geq 0.05$) compared to healthy females, as reported by Naidu et al. (2007). Table 2, also reports a similar finding, indicating elevated calcium levels in individuals diagnosed with cervical cancer. Calcium has the ability to directly interact with DNA bases, leading to heightened DNA base damage and an increased number of mutations in vitro. This process may contribute to the initiation and progression of carcinogenesis by deactivating or absenting specific tumor suppressor genes (Naidu et al., 2007).

The statistical analysis reveals a substantial decrease ($p \geq 0.05$) in serum zinc levels among females diagnosed with uterine cancer compared to those without the condition. This finding aligns with previous studies, including those by Naidu et al. and Karaca et al., which also reported decreased zinc levels in individuals with cervical cancer. Additionally, Al-Taee reported a significant drop in zinc concentration in the serum of patients with various forms of cancer compared to control groups. Zinc plays a protective role in cellular growth by controlling the integrity and stability of cell membranes. It is possible that cancer cells may utilize zinc from the bloodstream to support tumor growth and maintain membrane integrity, potentially explaining the observed zinc loss in individuals with uterine cancer (Beerheide et al., 1999).

Conclusion

This study sheds light on the intricate biochemical alterations associated with uterine cancer, highlighting significant reductions in urea, creatinine, vitamin C, and vitamin E levels, alongside elevated peroxynitrite and LDH activity. Additionally, serum calcium exhibited a notable rise, while zinc levels decreased substantially. These findings underscore the multifaceted nature of uterine cancer pathophysiology, emphasizing the importance of further research in diagnostics and therapeutics.

Author contribution

M.Q.A and W.S.A conceptualized, H.A.N analysed the data, M.Q.A,. M.A.D., Y.J.A performed experiments, M.Q.A,. W.S.A wrote and draft the article.

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Competing financial interests

The authors have no conflict of interest.

References

Abu-Rustum, N. R., Zhou, Q., Iasonos, A., Alektiar, K. M., Leitao, M. M., Chi, D. S., ... & Barakat, R. R. (2011). The revised 2009 FIGO staging system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered?. International Journal of Gynecologic Cancer, 21(3).

Bandera, E.V.; Gifkins, D.M.; Moore, D.F.; McCullough, M.L.; Kushi, L.H. (2009). Antioxidant vitamin and the risk of endometrial cancer adose-response metaanalysis. Cancer Causes and Control, 20(5), 699-711.

Beerheide, W.; Bernard, H.; Tan, Y.; Ganesan, A.; Rice, W.; Ting, A. (1990). Potential

Bhuvarahamurthy, V.; Balasubramanian, N.; Govindasamy, S. (1996). Effect of

Block, G. (1992). Fruit, vegetables and cancer prevention: A review of the epidemiological evidence. Nutr Cancer, 18 (1), 1-29. Buchanan, E.M.; Weinstein, L.C.; Hillson, C. (2009). Endometrial cancer. Am. Fam. Physician, 80(10), 1075-1080.

Boeckstaens, S., Dewalheyns, S., Heremans, R., Vikram, R., Timmerman, D., Van den Bosch, T., & Verbakel, J. Y. (2020). Signs and symptoms associated with uterine cancer in pre-and postmenopausal women. Heliyon, 6(11).

Boggess, J. F., Kilgore, J. E., & Tran, A. Q. (2020). Uterine cancer. In Abeloff's Clinical Oncology (pp. 1508-1524). Elsevier.

Bokhman, J. V. (1983). Two pathogenetic types of endometrial carcinoma. Gynecologic oncology, 15(1), 10-17.

Chen, L. M., Yang, P. P., Al Haq, A. T., Hwang, P. A., Lai, Y. C., Weng, Y. S., ... & Hsu, H. L. (2022). Oligo-Fucoidan supplementation enhances the effect of Olaparib on preventing metastasis and recurrence of triple-negative breast cancer in mice. Journal of Biomedical Science, 29(1), 70.

Clarke, M. A., Long, B. J., Morillo, A. D. M., Arbyn, M., Bakkum-Gamez, J. N., & Wentzensen, N. (2018). Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. JAMA internal medicine, 178(9), 1210-1222.

Cobbs, C.S.; Whisenhunt, T.R.; Wesemann, D.R.; Harkins, L.E.; Van Meir, E.G.; Samanta, M.(2003). Inactivation of Wild- Type p53 protein function by reactive oxygen and nitrogen species in malignant glioma cells. Can. Res., 63, 8670- 8673.

Devi, L. I., Ralte, L., & Ali, M. A. (2015). Serum biochemical profile of breast cancer patients. European Journal of Pharmaceutical and Medical Research, 2(6), 210-214.

drugs against cervical cancer. Zinc- ejecting inhibitors of the human papillomavirus Type 16E 6 oncoprotein. J. Formos Med. Assoc. Aug., 8, 677- 82.

Felix, A. S., Weissfeld, J. L., Stone, R. A., Bowser, R., Chivukula, M., Edwards, R. P., & Linkov, F. (2010). Factors associated with Type I and Type II endometrial cancer. Cancer Causes & Control, 21, 1851-1856.

Head, K. A. (1998). Ascorbic acid in the prevention and treatment of cancer. Altern Med Rev, 3(3), 174-186.

Karaca, F., Menteş, S., & Keskin, S. (2018). Evaluation of hematologic and biochemical parameters in patients with early stage uterine malignancy receiving radiotherapy. Eastern Journal of Medicine, 23(3).

Kimura, T., Kamiura, S., Yamamoto, T., Seino-Noda, H., Ohira, H., & Saji, F. (2004). Abnormal uterine bleeding and prognosis of endometrial cancer. International Journal of Gynecology & Obstetrics, 85(2), 145-150.

Kumar, M.; Birdi, A.; Gupta, Y.N.; Gupta, S. (1988). Serum lactate dehydrogenase isoenzymes alternation in carcinoma cervix uteri. Int. J. Gynaecol. Obset., 27(1), 91- 95.

M Bilal, K. (2013). Measurement of some biochemical parameters in serum of uterine cancer. Rafidain journal of science, 24(11), 37-44.

Mahfoudh AL-Musali Mohammed Abdulghani . (2017). Role of Angiogenesis on Uterine Fibroids Therapy: review. Angiotherapy, 1(1), pages 022-026.

Manju, V.; Sailaja, J.K.; Nalini, N. (2002). Circulating lipid peroxidation and antioxidant status in cervical cancer patients: acase- control study. Clinical Biochemistry, 35(8), 621- 625.

Merritt, L. L., Dean, J. A., & Willard, H. H. (Eds.). (1974). Instrumental methods of analysis. D. Van Nostrand Company.

Naidu, M.S.; Suryakar, A.N.; Swami, S.C.; Katkam, R.V.; Kumbar, K.M. (2007). Oxidative stress and antioxidant status in cervical cancer patients. Indian J. Clinical Biochemistry, 22(2), 140- 144.

Niki, E. (1991). Action of ascorbic acid as a scavenger of active and stable oxygen radicals. The American journal of clinical nutrition, 54(6), 1119S-1124S.

Pozzar, R. A., Hammer, M. J., Cooper, B. A., Kober, K. M., Chen, L. M., Paul, S. M., ... & Miaskowski, C. (2022). Stability of symptom clusters in patients with gynecologic cancer receiving chemotherapy. Cancer nursing, 45(4), E706-E718.

Prati, D., Taioli, E., Zanella, A., Torre, E. D., Butelli, S., Del Vecchio, E., ... & Sirchia, G. (2002). Updated definitions of healthy ranges for serum alanine aminotransferase levels. Annals of internal medicine, 137(1), 1-10.

radiotherapy and chemoradiotherapy on circulating antioxidant system of human uterine cervical carcinoma. Molecular and cellular Biochemistry, 158, 17- 23.

Rijke, D.; Trienekens, P.H. (1985). Variant expression of lactate dehydrogenase complex, interfering with isoenzyme analysis. Clin. Chem. Acta., 146, 135.

Schmeler, K. M., Soliman, P. T., Sun, C. C., Slomovitz, B. M., Gershenson, D. M., & Lu, K. H. (2005). Endometrial cancer in young, normal-weight women. Gynecologic oncology, 99(2), 388-392.

Seebacher, V., Schmid, M., Polterauer, S., Hefler-Frischmuth, K., Leipold, H., Concin, N., ... & Hefler, L. (2009). The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study. BMC cancer, 9, 1-5.

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. CA: a cancer journal for clinicians, 69(1), 7-34.

Smith, R. A., von Eschenbach, A. C., Wender, R., Levin, B., Byers, T., Rothenberger, D., ... & Eyre, H. (2001). American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers: Also: update 2001—testing for early lung cancer detection. CA: a cancer journal for clinicians, 51(1), 38-75.

ST, O. (1979). Selected methods for the determination of ascorbic acid in animal cells, tissues and fluids: Ascorbic acid analysis II. Determination. After derivatization with 2, 4-dinitrophenylhydrazine. Method Enzymol, 62, 3-11.

Stahl, W.; Sies, H. (1997). Antioxidant defense vitamins E and C and carotnoids. Diabetes, 46, 14- 18.

Subramanian, N.; Krishnan, H.M.; Venkatachalam, P.; Kamatchi, P.A.C. (2009). A study of lactate dehydrogenase (LDH) isoenzyme is a biochemical tumor marker in cervical carcinoma patients. Int. J. Hum. Genet, 9(1), 5- 12.

Thomas, J. H., & Gillham, B. (2013). Wills' biochemical basis of medicine. Elsevier.

Tietz, N.W. (1976). "Fundamentals of Clinical Chemistry". W. B. Saunders Company, Philadelphia.

Vanuffelen, B.E.; Van Derzec, J.; Dekoster, B.M. (1998). Biochem. J., pp.330-719 cited by Al-Zamely, O.M.; Al-Nimer, M.S.; Muslih, R.K. (2001). Detection the level of peroxy nitrite and related with antioxidant status in the serum of patient with acute myocardial infarction. Nat. J. Chem., 4, 625-637.

Varley, H.; Gowenlock, A.H.; Bell, M. (1980). "Practical Clinical Biochemistry". William Heinemann Medical Books LTD, London, Vol.1, pp. 222-225, 553-555.

Willard, H.H.; Meritt, L.L.; Dean, J.A. (1974). "Instrumental Methods of Analysis". 5th.ed., D. Van Nostrand Company, New York, pp. 350-388.