RESEARCH ARTICLE

Requests for Tumor Marker Tests in Turkey Without Indications and Frequency of Elevation in Benign Conditions

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Abstract

Aims: To investigate the incidence of ordering tests for tumor markers which are used in cancer diagnosis, follow-up treatment and detection of recurrence, the rate of elevation in benign diseases and which clinics order them frequently. Materials and Method: Data for the tumor markers carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), cancer antigen 125 (CA 125), cancer antigen 15-3 (CA 15-3) and alpha-fetoprotein (AFP) that were ordered by all the clinics in our Hospital between 2010 and 2011 were screened. When excluding repeated orders the results of 3,416 patients were available. It has been determined that in which benign diseases were the tumor markers frequently ordered and which of these conditions had high levels of them. Results: CA 19-9 was ordered for 1,858 patients 191 (10.3%) were malignant while 1667 (89.7%) were ordered in benign diseases. For CEA the total was 1,710, 226 (13.2%) malignant and 1484 (86.8%) benign, and for CA 125 1267, 111 (8.8%) malignant and 1156 (91.2%) benign. AFP was ordered for 1687 cases, 80 (4.7%) malignant but 1607 (95.3%) benign. CA 15-3 was ordered 1449 times, 174 (12%) for malignant and 1275 (88%) for benign diseases. In all cases, considerable proportions were positive. Conclusions: It was shown that clinicians frequently order tumor markers for benign conditions. The findings of this study has shown that tumor markers are used widely without indications as cancer screening tests.

Keywords: CA 19-9 - CEA - CA 125 - CA 15-3 - AFP - benign disease -Turkey

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Introduction

Although there are no specific tumor markers used in cancer screening, some markers can be used to assist in making a diagnosis and determining a prognosis. They can be used to follow up in cases where the diagnosis is cancer through monitoring the recurrence of the disease and/or evaluating the response to therapy (Duffy, 2001; Perkins et al., 2003). These markers are not specific as the number increases in multiple cases of cancer. In addition, they can act as false negatives, so their utilization in the diagnosis of cancer could be misleading. Clinicians often use these markers as a guideline. The markers can also be high in benign disease. Finding levels higher than normal through use of these markers in patients without cancer could lead to difficult situations and even cause psychological trauma and expensive research costs.

Carbohydrate antigen 19-9 (CA 19-9) is a marker that increases in pancreatic, biliary, hepatocellular and gastrointestinal malignancy. This marker is related to the Lewis blood group antigens and only patients who belong to the Le (α-β+) or Le (α+β-) blood groups will express the CA 19-9 antigen (Kannagi, 2007). The application of CA 19-9 as a universal biomarker is limited as Le (α-β-) phenotypes occurring in 5–10% of the population which lack enzyme 1, 4-fucosytl transferase that is required for antigen epitope production (Goonetilleke and Siriwardena, 2007).

Carcinoembryonic antigen (CEA) is a glycoprotein with a molecular weight of 180-200 kDa (Krupey et al., 1975). CEA is expressed in adenocarcinomas of the colon and other organs including the pancreas, lungs, prostate, urinary bladder, ovaries, and breasts; so it is commonly used as a marker of malignancy (Locker et al., 2006; Amayo and Kuria, 2009). Screening of this marker for adenocancer is very low sensitivity and specificity (Lim et al., 2009). It is also not recommended for use as a screening test for colorectal cancer (Locker et al., 2006). Cancer antigen 125 (CA 125) is a cell surface glycoprotein with 220-kDa expressed in more than 80% of non-mucinous epithelial ovarian cancers (Bast et al., 2005). Cancer antigen 15-3 (Ca 15-3) is a mucinous glycoprotein with a high molecular weight. It is used to track patients with breast cancer (Cheung et al., 2000). Alpha-fetoprotein (AFP) is an oncofetal glycoprotein consisting of a single chain and has a molecular weight of 70,000. It is released from liver cancer and germ cell tumors. However, this marker is low sensitivity for screening of hepatocellular cancer (Malaguarnera et al., 2010). Since tumor markers can increase in benign conditions, our aim is to determine

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the frequency and the purpose of ordering tumor markers in such cases.

Materials and Methods

The data of the tumor markers CA19-9, CEA, CA 125, AFP and CA 15-3 that were ordered by all the clinics in our Hospital between 2010 and 2011 were screened. The files of the patients where there was an incompatibility between the diagnosis and the ordered tumor markers were checked again by the clinician.

Incompatible results and incorrect records were excluded from the study. Repeated results in the same patient were excluded from the study, leaving 3,416 patients' records to be included in the study. Tumor markers were recorded if they were ordered singly or in groups. It was then determined for which diseases and from which clinics they were mostly ordered. In our laboratory, tumor markers were studied by the Chemiluminescent Microparticle Immunoassay (CMIA) method via the ARCHITECT I 2000 device. The reference values were Ca 19-9 0-37 U/ml, CEA 0-5 U/ml, CA125 0-35 U/ml, CA15-3 0-33.3 U/ml and AFP 0-8 ng/ml.

Statistical analysis and Ethic issue

The results were evaluated using SPSS 13 software with simple statistical tests (mean±standard deviation, frequency). It was determined in which benign diseases tumor markers were ordered and in which of them they were high. The study was approved by the local ethics committees, and informed consent from each participant was obtained (Approval number's: 2012/73).

Results

CA 19-9 was ordered for 1,858 patients and in 191 (10.3%) tumors were malignant, while in 1,667 (89.7%) they were benign. The benign occurrences were mostly for ovarian cysts (10.2%), anemia (7.3%) and abdominal pain (5.8%). CEA was ordered for 1,710 patients and in 226 of them (13.2%) malignant results occurred, whereas in 1,484 (86.8%) results were benign. It was mostly ordered in anemia (17.6%), abdominal pain (6.2%), and ovarian cysts (5.1%).

CA 125 was ordered for 1,267 patients and in 111 (8.8%) results were malignant, while in 1,156 (91.2%) results were benign. Benign cases were mostly for ovarian cysts (17%), anemia (7.3%) and menstrual disorders

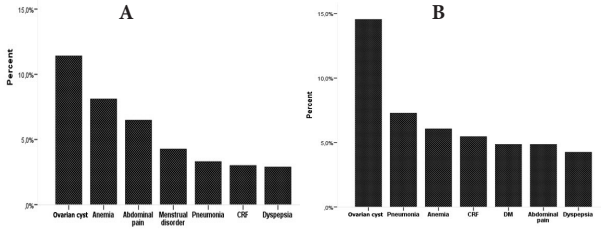

Figure 1. Rates of A) Ordering and B) Finding Ca19-9 in Benign Diseases. A) Ovarian Cyst 11.4%, Anemia 8.1%, Abdominal Pain 6.5%, Menstrual Disorder 4.3%, Pneumonia 3.3%, CRF 3.0%, Dyspepsia 2.9%. B) Ovarian Cyst 14.5%, Pneumonia 7.3%, Anemia 6.1%, CRF 5.5%, DM 4.8%, Abdominal Pain 4.8%, Dyspepsia 4.2%. CRF, chronic renal failure; DM, diabetes mellitus

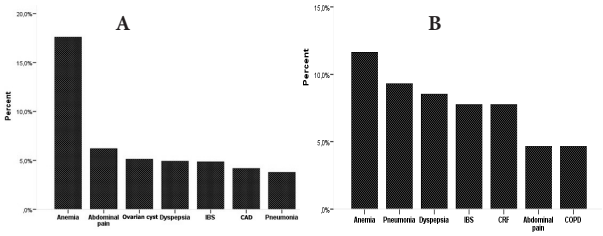

Figure 2. Rates of A) Ordering and B) Finding CEA in Benign Diseases. A) Anemia 17.6%, Abdominal Pain 6.2%, Ovarian Cyst 5.1%, Dyspepsia 4.9%, IBS 4.9%, CAD 4.2%, Pneumonia 3.8%. B) Anemia 11.6%, Pneumonia 9.3%, Dyspepsia 8.5%, IBS 7.8%, CRF 7.8%, Abdominal Pain 4.7%, COPD 4.7%. IBS, Irritable Bowel Syndrome. CRF, chronic renal failure; COPD, chronic obstructive pulmonary disease

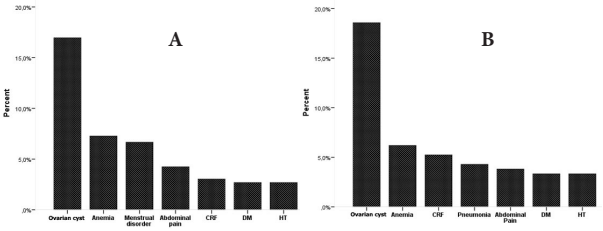

Figure 3. A) The Rates of A) Ordering and B) Finding Ca125 in Benign Diseases. A) Ovarian Cyst 17%, Anemia 7.3%, Menstrual Disorder 6.7%, Abdominal Pain 4.2%, CRF 3.0%, DM 2.7%, HT 2.7%. B) Ovarian Cyst 18.6%, Anemia 6.2%, CRF 5.2%, Pneumonia 4.3%, Abdominal Pain 3.8%, DM 3.3%, HT 3.3%. CRF, chronic renal failure; DM, diabetes mellitus; HT, hypertension

Table 1. The Incidences of Ordering Tumor Markers in Benign and Malign Diseases

Characteristic	CA 19-9	CEA	CA 125	AFP	CA 15-3
Age (years)	57±17	58±16	54±18	51±18	57±17
Gender (M/F)	679/1179	708/1002	248/1019	996/691	435/1014
The number of ordering	1858	1710	1267	1687	1449
Frequency of ordering in malign diseases (%)	191 (10.3)	226 (13.2)	111 (8.8)	80 (4.7)	174 (12)
Frequency of ordering in benign diseases (%)	1667 (89.7)	1484 (86.8)	1156 (91.2)	1607 (95.3)	1275 (88)
1. Ordered in BD (%)	Ovary cyst (10.2)	Anemia (17.6)	Ovary cyst (17)	Chronic hepatitis B (33.8)	Ovary cyst (9.9)
2. Ordered in BD (%)(%)	Anemia (7.3)	Abdominal pain (6.2)	Anemia (7.3)	Chronic hepatitis C (6.8)	Anemia (9)
3. Ordered in BD (%)	Abdominal pain (5.8)	Ovary cyst (5.1)	Menstrual disorder (6.7)	Anemia (4.7)	Abdominal pain (4.2)
The rate of finding tumor markers levels high in BD	9.9	8.7	18.2	9.5	6.4
1 Found to be elevated in BD (%)	Ovary cyst (14.5)	Anemia (11.6)	Ovary cyst (18.6)	Chronic hepatitis B (40.1)	Anemia (9.8)
2. Found to be elevated in BD (%)	Pneumonia (7.3)	Pneumonia (9.3)	Menstrual disorder (6.2)	Chronic hepatitis C (13.2)	Pneumonia (9.8)
3. Found to be elevated in BD (%)	Anemia (6.1)	Dyspepsia (8.5)	Anemia (6.2)	cirrhosis (8.6)	Pleural effusion (9.8)

*BD: benign disease

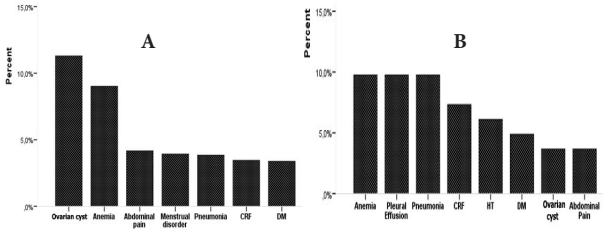

Figure 4. Rates of A) Ordering and B) Finding Ca15-3 in Benign Diseases. A) Ovarian Cyst 11.3%, Anemia 9.0%, Abdominal Pain 4.2%, Menstrual Disorder 3.9%, Pneumonia 3.8%, CRF 3.5%, DM 3.4%. B) Anemia 9.8%, Pleural Effusion 9.8%, Pneumonia 9.8%, CRF 7.3%, HT 6.1%, DM 4.9%, Ovarian Cyst 3.7%, Abdominal Pain 3.7%. CRF, chronic renal failure; HT, hypertension; DM, diabetes mellitus

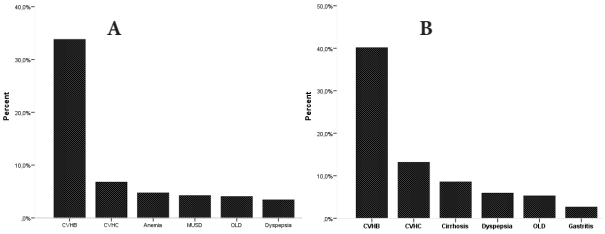

Figure 5. The Rates of A) Ordering and B) Finding AFP in Benign Diseases. A) CVHB 33.8%, CVHC 6.8%, Anemia 4.7%, MUSD 4.2%, OLD 4.0%, Dyspepsia 3.4%. CVHB, Chronic Viral Hepatitis B; CVHC, Chronic Viral Hepatitis C; MUSD, Male Urogenital System Disorder; OLD, Other Liver Disease. B) CVHB 40.1%, CVHC 13.2%, Cirrhosis 8.6%, Dyspepsia 5.9%, OLD 5.3%, Gastritis 2.8%. CVHB, chronic viral hepatitis B; CVHC, chronic viral hepatitis

(6.7%). AFP was ordered for 1,687 cases in which 80 (4.7%) were malignant and 1,607 (95.3%) were benign, mostly for chronic hepatitis B (33.8%), chronic hepatitis C, and anemia (4.7%). CA 15-3 was ordered 1,449 times, and 174 (12%) cases were malignant, while 1,275 (88%) were benign, mostly for ovarian cysts (9.9%), anemia, (9%) and abdominal pain (4.2%).

All the tumor markers were ordered for 288 patients and 15 of them were cancer cases, with the others being benign cases. The most common benign diseases for which tumor markers were ordered and in which of them they were elevated are shown in Table 1 and Figures 1a-b, 2a-b, 3a-b, 4a-b, and 5a-b.

The types of clinics that ordered tumor markers for benign diseases were as follows: for CA 19-9, obstetrics and gynecology (23.9%), internal medicine (19.9%), general surgery (17.2%), and gastroenterology (11.3%); for CEA, internal medicine (29.7%), gastroenterology (17.4%), general surgery (15.0%), and obstetrics and gynecology (11.1%); for CA 125, obstetrics and gynecology (35.0%), internal medicine (18.3%), general surgery (10.6%), and gastroenterology (7.3%); for CA 15-3, obstetrics and gynecology (24.4%), internal medicine (22.0%), general surgery (12.9%), and gastroenterology (8.3%); for AFP, infectious diseases (45.3%), gastroenterology (22.3%), internal medicine (14.0%), urology (6.6%), and obstetrics and gynecology (3.9%).

Discussion

Tumor markers are not specific and can be elevated even in benign conditions. They are not recommended to be used as screening tests. Not only can they be increased in benign cases (false positive), but they may also be low in malign cases (false negative). For example, CA 19-9 is known to be elevated in gastrointestinal tumors and has a sensitivity of 79-81% and a specificity of 82-90% in patients with asymptomatic pancreatic cancer (Ballehaninna and Chamberlain, 2011). It may be increased in benign cases such as acute cholecystitis, biliary obstruction and liver disease as well (Dogan et al., 2011; Yue et al., 2011). Even heavy tea consumption can lead to elevated serum CA19-9 levels (Howaizi et al., 2003). In our study, this marker was ordered mostly for ovarian cysts, anemia, and abdominal pain, and it was found to be high in benign conditions as ovarian cysts, pneumonia, and anemia. Previously studies showed that the level of CA 19-9 was found to be elevated in menstrual disorders, endometriosis, dermoid ovarian cysts, and ovarian chocolate cysts (Harada et al., 2002). Increased CA 19-9 levels in benign pulmonary events have also been reported (Pavai and Yap, 2003). In a previous study, the level of CA 19-9 was found to be elevated in 13 (3%) of patients with pneumonia (Marechal et al., 1988). It has been reported that in megaloblastic anemia the levels of CA 19-9 were not increased (Symeonidis et al., 2004). This marker was found to be sporadically high in patients with beta thalassemia (Christoforidis et al., 2007). Current literature does not confirm whether levels are elevated for this marker or not in patients with other types of anemia. On the other hand, this marker is ordered frequently in anemic patients, even though it may be sporadically elevated in this study. Also, CA 19-9 has been reported to be high in chronic renal failure and diabetes mellitus (Pavai and Yap, 2003; Yu et al., 2012). In current study show that the marker is increased these diseases.

CEA may increase in colorectal, lung, and ovarian cancers. CEA may rise in benign cases, especially in cigarette smokers (Sajid et al., 2008). It is also known to be elevated in chronic renal failure, senility, hypothyroidism, and other inflammatory conditions (Amino et al., 1981; Witherspoon et al., 1983). In current study, it has been found that doctors order CEA mostly in anemia, abdominal pain, and ovarian cysts. Additionally, it is found to be high in benign cases such as anemia, pneumonia, and dyspepsia. CEA was frequently indicating a false positive in non-malignant pleural effusions (Amino et al., 1981). It has been found to be elevated in 14.7% of parapneumatic effusions (Ryu et al., 2003). The CEA level was found to be higher in patients with pneumonia than in healthy patients (Shiota et al., 1989). Literature confirms that the CEA level does not increase in megaloblastic anemia (Symeonidis et al., 2004). In iron deficiency anemia, the CEA level was found to be elevated in gastrointestinal-related lesions (peptic ulcers, celiac disease, familial polyposis coli, etc) (Serefhanoglu et al., 2010).

CA 125 is used to track ovarian cancer and may be high in many benign cases. It may be elevated during menstruation, pregnancy, in endometriosis, pelvic inflammatory disease, liver disease, and lung disease (Escudero et al., 2011). In this study, it was found that this marker was ordered mostly in ovarian cysts, anemia, and menstrual disorders, and it was elevated mostly in ovarian

cysts, menstrual disorders, and anemia. CA 125 was high in cases of endometriosis and was recommended as a biomarker for the diagnosis of endometriosis (Szubert et al., 2012). It has also been reported to be elevated in cases of benign ovarian cysts. In a study of postmenopausal women with ovarian cysts, CA 125 (levels<35 IU/ml) was found to be a useful marker that is significantly related to benign cysts (Dikensoy et al., 2007). In follow-up treatment for ovarian cysts, in cases where levels are <5 cm or CA 125 is high, the decision to operate may be taken with regard to the patient's age and menstrual status (Knudsen et al., 2004). As a result of being retrospective, our study has revealed no information about the incidence of malignancy in ovarian cyst patients with high CA 125 levels or whether or not they underwent operations. This marker does not increase in megaloblastic anemia (Symeonidis et al., 2004). Literature does not confirm whether CA 125 levels are elevated or not in patients with other types of anemia. It is known to be increased in heart failure and renal failure (Xiaofang et al., 2007; Topatan and Basaran, 2011). Our study show that is similar results of previously studies.

CA 15-3 is used frequently in follow-up treatment of breast cancer and in showing metastasis. In this study, it was ordered mostly in cases of ovarian cysts, anemia, and abdominal pain. It has been found to be high in benign conditions, especially in cases of anemia, pneumonia, and pleural effusions. CA 15-3 was found to be high in megaloblastic anemia (Triantafillidis et al., 2002; Symeonidis et al., 2004). This marker was found to be elevated in patients with beta thalassemia (Symeonidis et al., 2006). There was no information about the relation among this marker, iron deficiency, and chronic anemia. CA 15-3 indicated a false positive in 5% of pneumonia cases (Marechal et al., 1988). The level of CA 15-3 was high in malignant pleural effusions, but it was normal in benign pleural effusions (Topolcan et al., 2007; Wagner et al., 2007). In this study, the level of CA 15-3 was found to be higher than normal in 82 cases with benign pleural effusion. In 13 of these cases, it was more than three times higher, and in 17 of these cases was more than 50 U/ml higher. However, most of them were between normal range and 50 U/ml. Excessive increases may be reported in sporadic cases. On the other hand, the etiology of these was not researched in this study. High results may be found regarding the etiology.

AFP is a marker that increases in liver cancer and germ cell tumors. AFP was found to be high in benign liver diseases such as hepatitis and cirrhosis (Kobeisy et al., 2012). The levels between 15-100 ng/ml were found in 25% of acute hepatitis cases, levels >100 ng/ml were found in 4.9% of chronic liver disease (Forones et al., 1995). In another study, AFP levels were found to be high in patients with or without cirrhosis (Collazos et al., 1992). In this study, it was ordered mostly in cases of chronic hepatitis B, hepatitis C, and anemia. Among benign conditions it was found to be high mostly in hepatitis B, hepatitis C and cirrhosis. AFP is used frequently as a screening test for hepatocellular cancer, in cirrhosis, hepatitis B, and hepatitis C infections.

Current study has revealed that tumor markers were clearly ordered without indications. Recommendations include using CA 125 in discriminating between benign and malign ovarian cysts, CA 15-3 in discriminating between benign and malign pleural effusions, and AFP to screen hepatocellular cancer in chronic hepatitis B, hepatitis C, and cirrhosis. However, in our study, tumor markers were ordered in nonspecific cases, mostly for anemia, dyspepsia, abdominal pain, ovarian cysts, chronic renal failure, and menstrual disorders. Tumor markers were ordered in cases with abdominal pain mostly without researching the etiology. Similarly they were ordered to patients with anemia without considering the etiologic factors. Particularly in the elderly population, the rate of ordering these markers was found to be high. It is thought that doctors are more likely to order these markers not to miss underlying cancer and to detect and treat it early.

The distribution of the types of clinics according to the ordering of tumor markers was found to be mostly obstetrics and gynecology, internal medicine, gastroenterology, and general surgery clinics. This may be due to these clinics frequently encountering cancer cases, such as breast cancer, ovarian cancer, and gastrointestinal system cancers. Unlike other markers, AFP was frequently ordered by infectious diseases clinics and often by urology clinics. It was observed that infectious diseases clinics ordered this marker for following up cases of chronic viral hepatitis, whereas urology clinics used this marker in cases of disease in the male urogenital system and in cases of infertility. All markers were ordered for 288 patients, while they were ordered separately in single, double or triple. It has been concluded that clinicians use these markers as screening tests without considering the diagnoses.

In conclusion, the results of the study have shown that tumor markers may often be high, even in benign cases. This is time-consuming for doctors and can cause severe trauma in patients who are misdiagnosed with or unnecessarily tested for cancer. Furthermore, the radiation that is given off during computerized tomography scans may lead to cancer in healthy subjects in the future. Even a single shot of radiation during computerized tomography may be enough to cause cancer. Strict malpractice laws, patients fear of cancer, and the establishment of healthcare organizations such as cancer screening centers may lead to the unnecessary ordering of tumor marker tests. Ordering tumor marker tests without a clear indication of need is not only high in cost, but it can also lead to anxiety for patients.

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References

Amayo AA, Kuria JG (2009). Clinical application of tumour markers: a review. *East Afr Med J*, **86**, 76-83.

Amino N, Kuro R, Yabu Y, et al (1981). Elevated levels of circulating carcinoembryonic antigen in hypothyroidism. *J Clin Endocrinol Metab*, **52**, 457-62.

Ballehaninna UK, Chamberlain RS (2011). Serum CA 19-9 as a biomarker for pancreatic cancer-a comprehensive review.

Indian J Surg Oncol, **2**, 88-100.
Bast RC Jr, Badgwell D, LuZ, et al (2005). New tumor markers: CA125 and beyond. *Int J Gynecol Cancer*, **15**, 274-81.
Cheung K, Graves CR, Robertson JF (2000). Tumor marker measurements in the diagnosis and monitoring of breast cancer. *Cancer Treat Rev*, **26**, 91-102.
Christoforidis A, Lefkou E, Vlachaki E, et al (2007). Evaluation of serum tumour markers concentrations in patients with homozygous beta-thalassaemia in relation to demographical, clinical and biochemical parameters. *Ann Hematol*, **86**, 837-41.
Collazos J, Genolla J, Ruibal A (1992). Preliminary study of alpha-fetoprotein in nonmalignant liver diseases. A clinico-biochemical evaluation. *Int J Biol Markers*, **7**, 97-102.
Dikensoy E, Balat O, Ugur MG, Ozkur A, Erkilic S (2007). Serum CA-125 is a good predictor of benign disease in patients with postmenopausal ovarian cysts. *Eur J Gynaecol Oncol*, **28**, 45-7.
Dogan UB, Gumurdulu Y, Golge N, Kara B (2011). Relationship of CA 19-9 with choledocholithiasis and cholangitis. *Turk J Gastroenterol*, **22**, 171-7.
Duffy MJ (2001). Clinical uses of tumor markers: a clinical review. *Crit Rev Clin lab Sci*, **38**, 225-62.
Escudero JM, Auge JM, Filella X, et al (2011). Comparison of serum human epididymis protein 4 with cancer antigen 125 as a tumor marker in patients with malignant and nonmalignant diseases. *Clin Chem*, **57**, 1534-44.
Forones NM, Queiroz LA, Ferraz ML, Parise ER (1995). Alphafetoprotein in hepatic tumours and benign liver diseases. *Rev Assoc Med Bras*, **41**, 91-3.
Goonetilleke KS, Siriwardena AK (2007). Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol*, **33**, 266-70.
Harada T, Kubota T, Aso T (2002). Usefulness of CA19-9 versus CA125 for the diagnosis of endometriosis. *Fertil Steril*, **78**, 733-9.
Howaizi M, Abboura M, Krespine C, et al (2003). A new cause for CA19.9 elevation: heavy tea consumption. *Gut*, **52**, 913-4.
Kannagi R (2007). Carbohydrate antigen sialyl Lewis a—its pathophysiological significance and induction mechanism in cancer progression. *Chang Gung Med J*, **30**, 189-209.
Knudsen UB, Tabor A, Mosgaard B, et al (2004). Management of ovarian cysts. *Acta Obstet Gynecol Scand*, **83**, 1012-21.
Kobeisy MA, Morsy KH, Galal M, et al (2012). Clinical significance of elevated alpha-foetoprotein (AFP) in patients with chronic hepatitis C without hepatocellular carcinoma in upper EGYPT. *Arab J Gastroenterol*, **13**, 49-53.
Krupey J, Wilson T, Freedman SO, Gold P, (1972). The preparation of purified carcinoembryonic antigen of the human digestive system from large quantities of tumor tissue. *Immunochemistry*, **9**, 617-22.
Lim YK, Kam MH, Eu KW, (2009). Carcinoembryonic antigen screening: how far should we go? *Singapore Med J*, **50**, 862-5.
Locker GY, Hamilton S, Harris J, et al (2006). ASCO. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol*, **24**, 5313-27.
Malaguarnera G, Giordano M, Paladina I, et al (2010). Serum markers of hepatocellular carcinoma. *Dig Dis Sci*, **55**, 2744-55.
Marechal F, Berthiot G, Deltour G (1988). Serum levels of CA-50, CA-19-9, CA-125, CA-15.3, enolase and carcino-embryonic antigen in non neoplastic diseases of the lung. *Anticancer Res*, **8**, 677-80.
Pavai S, Yap SF (2003). The clinical significance of elevated levels of serum CA 19-9. *Med J Malaysia*, **58**, 667-72.
Perkins GL, Slater ED, Sanders MD, Prichard JG (2003). Serum tumor markers. *Am Fam Physician*, **68**, 1075-82.
Ryu JS, Lee HJ, Cho JH, Han HS, Lee HL (2003). The implication of elevated carcinoembryonic antigen level in pleural fluid of patients with non-malignant pleural effusion. *Respirology*, **8**, 487-91.
Sajid KM, Chaouachi K, Mahmood R (2008). Hookah smoking and cancer: carcinoembryonic antigen (CEA) levels in exclusive/ever hookah smokers. *Harm Reduct J*, **5**, 19.
Serefhanoglu S, Buyukasik Y, Emmungil H, et al (2010). Identification of clinical and simple laboratory variables predicting responsible gastrointestinal lesions in patients with iron deficiency anemia. *Int J Med Sci*, **8**, 30-8.
Shiota Y, Furuya K, Kitade M, Ueda N, (1989). CEA and CA19-9 in BALF from patients with idiopathic interstitial pneumonia. *Nihon Kyobu Shikkan Gakkai Zasshi*, **27**, 887-93.
Symeonidis A, Kouraklis-Symeonidis A, Apostolopoulos D, et al (2004). Increased serum CA-15.3 levels in patients with megaloblastic anemia due to vitamin B12 deficiency. *Oncology*, **67**, 359-67.
Symeonidis A, Kouraklis-Symeonidis A, Constantinidou I, et al (2006). Increased CA-15.3 levels in the serum of patients with homozygous beta-thalassaemia and sickle cell/beta-thalassaemia. *Br J Haematol*, **133**, 692-4.
Szubert M, Suzin J, Wierzbowski T, Kowalczyk-Amico K (2012). CA-125 concentration in serum and peritoneal fluid in patients with endometriosis - preliminary results. *Arch Med Sci*, **8**, 504-8.
Topatan B, Basaran A, (2011). CA-125 and heart failure: reiteration and reappraisal. *Int J Cardiol*, **153**, 76-8.
Topolcan O, Holubec L, Polivkova V, et al (2007). Tumor markers in pleural effusions. *Anticancer Res*, **27**, 1921-4.
Triantafillidis JK, Cheracakis P, Konstantellou E, Hyphantis T, (2002). Increased serum levels of the tumor marker CA 15-3 on patients with pernicious (Biermer) anemia. *Oncology*, **63**, 306-7.
Wagner IC, Guimaraes MJ, da Silva LK, de Melo FM, Muniz MT (2007). Evaluation of serum and pleural levels of the tumor markers CEA, CYFRA21-1 and CA 15-3 in patients with pleural effusion. *J Bras Pneumol*, **33**, 185-91.
Witherspoon LR, Shuler SE, Alyea K, Husserl FE (1983). Carcinoembryonic antigen: assay following heat compared with perchloric acid extraction in patients with colon cancer, non-neoplastic gastrointestinal diseases, or chronic renal failure. *J Nucl Med*, **24**, 916-21.
Xiaofang Y, Yue Z, Xialian X, Zhibin Y (2007). Serum tumour markers in patients with chronic kidney disease. *Scand J Clin Lab Invest*, **67**, 661-7.
Yu H, Li R, Zhang L, et al (2012). Serum CA19-9 level associated with metabolic control and pancreatic beta cell function in diabetic patients. *Exp Diabetes Res*, **2012**, 745189.
Yue T, Maupin KA, Fallon B, et al (2011). Enhanced discrimination of malignant from benign pancreatic disease by measuring the CA 19-9 antigen on specific protein carriers. *PLoS One*, **6**, 29180.