The Role of Serum Tumour Markers in Gynaecological Cancers

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Not all serum tumour markers are reliable in screening for gynaecological cancers. Furthermore, there are some cancers that are better detected by simple biopsy. Most markers, however, are useful in monitoring of treatment or recurrence, or in determining prognosis.

Tumour markers are substances that can be detected in blood or tumour tissue and signify the presence of a tumour. A 'good' serum tumour marker should allow the determination of the volume and extent of a tumour's spread. An 'ideal' serum tumour marker should be of use in the screening and diagnosis of cancers, in establishing a prognosis and in monitoring the subsequent treatment of disease and its recurrence. Many existing serum tumour markers, and particularly those of gynaecological cancers, are far from ideal.

Table 1: Clinical Sensitivity, Specificity, Positive Predictive and Negative Predictive Values of a Serum Tumour Marker in Association with its Cancer.

	Cancer		
	Present	Absent	Total
Tumour marker positive	a	b	e
negative	c	d	f
Total	g	h	

Sensitivity = a/ (a+c) or g. Specificity = d/ (b+d) or h. Positive predictive value = a/ (a+b) or e. Negative predictive value = d/(c+d) or f.

Sensitivity and Specificity

An ideal tumour marker should only be present in patients with the specific cancer associated with that marker. A measure of the percentage of patients with a particular cancer that will be correctly identified by screening for a particular tumour marker is termed the marker's sensitivity. This is defined as, true positive/(true positive + false negative) (table 1). For example, the sensitivity of CA125 as a marker of epithelial ovarian cancer is 80% which means that in 100 patients with epithelial ovarian cancer, the probability is that 80 will have a raised CA125 level (true positive) while 20 will have a normal CA125 level (false negative).

The specificity of a serum tumour marker is another matter. This is the percentage of healthy patients that will be correctly excluded by screening using a particular marker and is defined as the true negative/(true negative + false positive). For example, the specificity of CA125 is 95% which means that in 100 patients with no epithelial cancer, the probability is that 95 patients will have normal

CA125 levels (true negative) but 5 patients will show raised levels (false positive). These false positive results may be due to pregnancy, menstruation, benign neoplasm or other malignancies such as carcinoma of the breast.[1] An ideal serum tumour marker should have both a high sensitivity and a high specificity.

The intrinsic production of a serum tumour marker affects its sensitivity and specificity. However, sensitivity and specificity may be adjusted artificially by using different cutoff levels. For example, in screening for ovarian cancer, to improve the specificity, (and to avoid unnecessary laparotomy,) a cutoff level of 65 IU/L is accepted as the upper limit of normality by some researchers even though the 95th centile of CA125 concentration in a normal population is 35 IU/L. Conversely, the cutoff level for normality could be lowered to 30 IU/L to improve the sensitivity at the expense of specificity (although fewer diseased patients would be 'missed', more false positive results would be obtained). Hence, in choosing a 'normal' cutoff level for a serum tumour marker, a balance between sensitivity and specificity has to be considered. In general, either the 95th centile of, or 2 standard deviations above the mean serum tumour marker level of a normal population is used as the cutoff to distinguish 'normal' and 'raised' tumour marker levels.

Predictive Value

The practical value of a serum tumour marker, especially if it is to be used for screening, depends on the prevalence of the cancer in association with the tumour marker. The positive predictive value (PPV) of a serum tumour marker, a measure of the reliability of a positive result, is defined as the true positive/(true positive + false positive). This value is dependent on the prevalence of the cancer in question. For example, if the prevalence of a particular cancer is 4 in 1000, and a serum tumour marker used for screening has a sensitivity of 75%, the marker level will be raised in 3 'true positive' patients. Furthermore, if the specificity of the serum tumour marker is 99%, 10 'false positive' patients would have a raised level in the absence of the cancer. The positive predictive value of this serum tumour marker in association with its cancer is 3/(3+10) =.23%. If the prevalence of a second cancer is 40/1000, i.e. ten times more common than the previous one, and is to be screened with a marker with a similar sensitivity and specificity, 30 'true positive' patients with cancer will have a raised serum tumour marker and 10 'false positive' patients will have a raised level without cancer. The positive predictive value of this serum tumour marker in association with its cancer is 30/(30+10) = 75%. It can be seen that, with the same sensitivity and specificity, the PPV of one serum tumour marker in association with its cancer can be 3 times higher than another when the prevalence of its associated cancer is 10 times higher. Conversely, the negative predictive value (NPV), the percentage of patients that do not have a raised marker level and do not have the cancer being screened, is defined as true negative/(true negative + false negative) and is higher in cancers with lower prevalence rates. The NPV of the first example with low prevalence is 99.9% and that of the higher prevalence cancer is 99%. Hence, the value of a serum tumour marker in association with a particular cancer should be evaluated in terms of its sensitivity, specificity, positive and negative predictive values.

Laboratory Assay of Serum Tumour Marker—Sensitivity and Specificity

The evaluation of a serum tumour marker is still not complete if based only on clinical sensitivity, specificity, PPV and NPV. The sensitivity and specificity of the assay must also be considered. Most serum tumour markers are assayed using antibodies, monoclonal or polyclonal, raised against antigens either produced by or in association with the tumour.

The sensitivity of the assay relies on the strength of antibody-antigen binding as well as on the method used to detect the bound complex

eg. radioisotope/chemiluminence assay. A sensitive test can detect very low levels of a tumour marker.

The specificity of an assay depends on how specific is the binding of the antibody to the antigen. Nonspecific binding means that an antibody will also bind to antigens of other proteins as well as to the tumour marker. In this case an assay will therefore not reflect the true level of the marker being measured. Polyclonal antibodies tend to be less specific. An assay implementing two antibodies that 'sandwich' the antigens of a serum tumour marker is more sensitive and specific especially if monoclonal antibodies are used.

An evaluation of the sensitivity and specificity of the proposed assay for each serum tumour marker should be made. Assays with poor sensitivity or specificity should not be used.

Screening for Gynaecological Malignancies

Screening aims to detect a precancerous or early stage of a disease among an asymptomatic population. Screening programmes for cervical cancer are the most successful in the field of gynaecology. However, although more than 60% of cases of squamous cell carcinoma have a raised squamous cell carcinoma antigen (SCC) level,[2] the sensitivity and specificity of SCC as a tumour marker is still far from ideal.

Serum tumour markers have no place at all in screening for endometrial cancer since no marker has a sensitivity of more than 50%. Our study in endometrial cancer concluded that the percentage of patients showing raised levels of different markers were as follows, CA125, 31%; CA 15.3, 26%; CA 19.9, 26%; CEA, 21% and for tissue polypeptide antigen (TPA) 26% of patients showed a raised level.[3] Other studies also showed similar percentages of raised serum marker levels in endometrial cancer.[4-6] In spite of this, presentation with vaginal bleeding in the initial stages of the disease often enables an early diagnosis to be made. Vulvar cancer is also best detected by clinical examination especially in patients complaining of pruritus vulva or abnormal bleeding. SCC is raised in only 15% of primary squamous cell carcinoma of the vulva.[7]

The use of tumour markers in the screening of ovarian cancer is still under evaluation. In a study by Jacobs et al,[8] 22,000 women aged 45 were screened using serum CA125 and ultrasound. Though the specificity of the screening reached 99.9%, the sensitivity was only 78.6% with a positive predictive value of 26.8%. The sensitivity of the screening programme dropped to 57.9% after 2 years.

CA125, though raised in more than 80% of epithelial cancers, is not a good serum tumour marker to use in screening. For example, the early diagnosis of ovarian cancer by using CA125 alone is impractical as only 50% of stage I disease is accompanied by a raised CA125 level.[9] Furthermore, CA125 is raised in nonmalignant conditions such as menses, pregnancy and in benign diseases such as fibroids, endometriosis. The use of ultrasound especially transvaginal ultrasonography in addition to CA125 may improve the sensitivity and specificity of the screening process.[10] However, in endometriosis, in addition to a raised CA125 level, a benign adnexal mass may be detected on ultrasound examination and misinterpreted as a malignant condition. The use of Doppler may improve the sensitivity or specificity of the ultrasound examination.[11,12] However, a resistance index of < 0.4 was detected in 43% of benign tumours and 25% of normal ovaries.[13] Further study is required to evaluate the practical use of Doppler in the screening of ovarian cancer. At present, a combined CA125 assay and ultrasonogram is not an effective screening method for ovarian cancer and should not be employed for clinical purposes outside of a research setting. Further studies are still in progress and tumour markers other than CA125 are being used to try to improve the sensitivity of screens.

The only serum tumour marker that can be reliably used in screening for gynaecological malignancies

is human chorionic gonadotrophin (hCG). In patients with hydatidiform mole, serum hCG should be monitored weekly following evacuation of the molar pregnancy until it returns to a normal level. Monitoring should continue for a year.[14] The serum hCG enables an early diagnosis of persistent gestational trophoblastic disease (PGTD) to be made. This is a disease that shows a good response to chemotherapy especially in its early stages. In patients with molar pregnancy, hCG is an ideal marker for PGTD.

Table 2: Summary of the Role of Common Serum Tumour Markers in Gynaecological Malignancies

	Tumour markers and malignancies			
	CA125 Ovarian Ca	SCC Cervical Ca	AFP Germ cell	hCG PGTD
Screening	+USS research	no use	no use	in mole
Diagnosis	helpful	no use	helpful	essential
Monitoring of treatment	80 to 90% correlation	80 to 90% correlation	high	near 100%
Monitoring of recurrence	80 to 90% correlation	80% correlation	high	diagnostic
Prognosis	rate of fall	prePx postRT	--	yes

Diagnosis of Gynaecological Malignancies

Generally, a good serum tumour marker should aid in the diagnosis of cancer. An exception is with cervical and vulvar cancers where tumours can be more easily assessed and diagnosed with a simple biopsy. Similarly, the diagnosis of endometrial cancer relies on either an endometrial aspiration or a dilation and curettage, again the use of tumour markers will confer no additional benefit. In ovarian cancer, a raised CA125 in association with an adnexal mass may be due to endometriosis or a benign tumour e.g. fibroid. There is limited application for CA125 in the diagnosis of early ovarian cancer. However, in patients with pelvic masses and marked ascites, a high level of serum CA125 is suggestive of ovarian cancer. Nevertheless, other primaries such as gastrointestinal or breast cancer have to be excluded since a raised CA125 could also be attributable to these cancers.

In young girls with adnexal masses, a raised alpha-fetoprotein (AFP) or hCG is more suggestive of endodermal sinus tumour or mixed germ cell tumour. Preoperative counselling should favour a more conservative approach if either of these tumours is suspected. A granulosa cell tumour of the ovary should be suspected if a high serum oestrogen level is detected especially in prepubertal or postmenopausal women. In PGTD, a stationary or rising serum hCG level after termination of a molar pregnancy confirms the diagnosis.

Though these tumour markers aid in the diagnosis of tumours, knowledge of other causes of raised tumour marker levels is essential to avoid an incorrect diagnosis. Normal pregnancy has to be excluded before PGTD is diagnosed by a rising serum hCG level. A high AFP level may be due to the presence of liver disease. An increased CA125 level may be due to extra-ovarian malignancies or even to a benign condition. The whole clinical picture must be considered when a raised serum tumour marker is detected before a diagnosis is made.

Monitoring of Treatment and Recurrence

Serum CA125 is used widely in monitoring the response to treatment of epithelial ovarian cancer. The correlation of a change in the levels of the marker with the disease's clinical course is 80 to 90%.[15,16] However, although a rising level of CA125 is almost invariably associated with progressive disease, a normal CA125 does not always signify absence of disease.[17] Consequently, other investigative measures are required to find out whether the patient has had a complete response to chemotherapy. A rising CA125 level in ovarian cancer affords an early indication that chemotherapy is ineffective and should be discontinued. At present, a study is attempting to discover if a change of treatment based on rising CA125 alone (in the absence of clinical disease) will benefit the patient. CA125 is also used to monitor recurrent disease. Rise of CA125 precedes clinical detection of recurrence by a median interval of 4 months.[18] Again, whether immediate treatment with chemotherapy in the absence of clinical disease will be of benefit to the patient is still under investigation.[19]

AFP is used to monitor the effect of chemotherapy on endodermal sinus tumours and their recurrence, its level has a high correlation with the clinical course of the disease. The number of courses of chemotherapy administered will be dictated by the AFP level. However, in patients with mixed germ cell tumours, such as dysgerminoma, other parameters of clinical assessment of tumour response are required since these tumours do not produce AFP.

The level of serum SCC also shows a high correlation (87%) with the progression of disease in patients receiving chemotherapy for cervical cancer.[20] Though chemotherapy is not a standard treatment for cervical cancer, it is useful in controlling symptoms and slowing the progression of the disease. Monitoring serum SCC levels will provide an early opportunity to stop or change an ineffective toxic therapy. The change of serum SCC levels during radiotherapy is of less help in monitoring radiotherapy response. However, it has been noted that patients with a raised serum SCC level after completion of radiotherapy had poorer prognoses.[21] A rise in serum SCC precedes clinical recurrence by a median interval of 3 months.[22] The sensitivity and specificity of SCC level assays with respect to tumour recurrence were 75 and 98% respectively. However, the clinical benefit of this type of SCC level assay is probably limited since most of the recurrence in cervical cancer is too advanced for curative treatment.

In PGTD, serum hCG is used to monitor treatment response and recurrence of disease. Depending on the rate of fall of the serum hCG level one or two courses of chemotherapy are prescribed after the hCG level has returned to normal. A rise of serum hCG after complete remission signifies a recurrence provided pregnancy is excluded.

Thus, in gynaecological cancers, the most effective role of serum tumour markers is in monitoring progression and therapy.

Prognosis

Pretreatment CA125 level is not of prognostic significance, however but the rate of fall or half-life of CA125 after chemotherapy is.[23-25] Pretreatment and postradiotherapy raised serum SCC level also has prognostic significance.[22,26] Some studies have shown that in stage I cervical cancer, patients with raised SCC levels had a poorer outcome and required more aggressive treatment.[27] Though only 26% of patients with endometrial cancer had a raised CA15.3 level, these patients had poorer prognoses.[3] Pretreatment serum hCG level has prognostic significance and has been incorporated into the 1992 FIGO staging system. Serum hCG levels of more than 10 000 IU/L are dangerous and their detection may influence the chemotherapy protocol used. The secondary role of serum tumour markers in gynaecological cancers is their prognostic value.

Conclusions

The only gynaecological cancer serum tumour marker that is anywhere near ideal is serum hCG in the management of PGTD. Most other markers are useful in the monitoring of treatment or recurrence and as a prognostic indicator (Table 2). Since there is no ideal marker for screening of solid gynaecological cancers, serum tumour markers should not be assayed blindly. Undue anxiety and unnecessary investigations caused by a false positive testing can be avoided if serum tumour markers are used wisely. The use of serum tumour markers should be left to specialists with a full knowledge of the sensitivity and specificity of an individual marker and its associated malignancy.

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