Decision Making between Tumor Marker & PET Scan IF Met with High Tumor Marker/Normal PET

St .Maltin de porres

Hospital,

Chia-yi city

Department of nuclear medicine

PET Cencer

CHAO YANG MEN

---share by two cases

Welcome to this bimonthly meeting of nuclear medicine 9/13 pm

WHY I USE THIS TOPIC FOR THIS MOMENT?

What kind of relation between tumor marker and PET scan in cancer patients?

► As for breast cancer patients, CA-153(23 U/Ml) and CEA(5 ng/Ml) has 64.8; 61.8% for PPV in all PET/CT f/u patient for comparison.

As for f/u post op for 8 years patients:93 motalities had 47 tumor marker rise. (649 PET with 250 regular tumor marker f/u developing breast cancer). As for f/u 142 disease free patient had 27 patients with elevated in tumor marker had long term in surveillance value (p<0.001), Ann Breast Surg 2019;3;30.

There must be MODERATE relationship between tumor marker and PET scan.

PET metabolic volume" was obtained by multiplying the "PET volume" by the mean SUV of the tumor. All recurrent or metastatic lesions were single or multiple lesions of measurable size (axial diameter > 1 cm, minimum "PET volume" 3.5 cm3), and were verified by operation or by other imaging modalities (CT or MRI). There was a linear associations between "PET volume" and serum CEA level. Further regression analysis by least squares showed a highly significant model with an equation of volume = 41.2 + 0.471 CEA (r2 = 0.629). However, no such association was found between "PET metabolic volume" and serum CEA level according to the residual normality test. In conclusion, "PET volume" measured by FDG PET and serum CEA level in colorectal cancer are significantly correlated. Tumor volume determined by FDG PET can be used as an effective marker of tumor burden in postoperative patients with colorectal carcinoma.

r2 indicating pearson correlation coefficient: high correlated means >than 0.5.

Annals of Nuclear Medicine volume 19, pages 123-129 (2005)

Efficiency of the combination of 18F-FDG PET/CT, CEA, and CA199 in detection of colorectal cancer and monitoring postoperative tumor metastasis

Xiaolin Wang1 Received March 26, 2018; Accepted May 2, 2018; Epub July 15, 2018; Published July 30, 2018

Int J Clin Exp Med 2018;11(7):7254-7259

SUV≥2.5 was adjudicated as the presence of malignant tumor. Serum CEA>3.4 ng/mL and CA199>27 U/mL were adjudicated as positive CRC results. In the combined detection by 18F-FDG PET/CT, CEA, and CA199, SUV equal to or greater than 2.5 and positivity of CEA and CA199 were defined as presence of a malignant tumor. The diagnostic efficiency of combining 18F-FDG PET-CT, CEA, and CA199 in detecting CRC and its value in monitoring tumor metastasis were analyzed. Results: The results of SUV, CEA, and CA199 in CRC patients were remarkably higher than those in normal volunteers (all P<0.001).SUV, CEA, & CA199 were highly expressed in patients. Accuracy of the three-modality combination in detection of CRC was 92.23%, sensitivity was 96.87%, and specificity was 87.00%, which were superior to those of the single modality (P<0.05). Moreover, the three-modality combination had high sensitivity & specificity for monitor ing postoperative metastasis of tumors. Conclusion: Combination of 18F-FDG PET-CT, CEA, and CA199 in the diagnosis of CRC has higher accuracy, sensitivity, and specificity, and it was effective in monitoring postop cases.

腫瘤指標tumor marker有以下功能

PET/CT benefit points

- 1.在無症狀之族群篩檢出早期癌症
- 2.診斷癌症
- 3.判斷預後
- 4.監測抗癌治療的反應
- 5. 偵測癌症復發

使用腫瘤指標的優點:

- 1.造成病人的不便與傷害小
- 2.可以短時間內大量檢測
- 3.判讀客觀
- 4.相對價格便宜

使用腫瘤指標的缺點:

- 1.缺乏特異性
- 2.難以早期診斷(早期敏感度低)

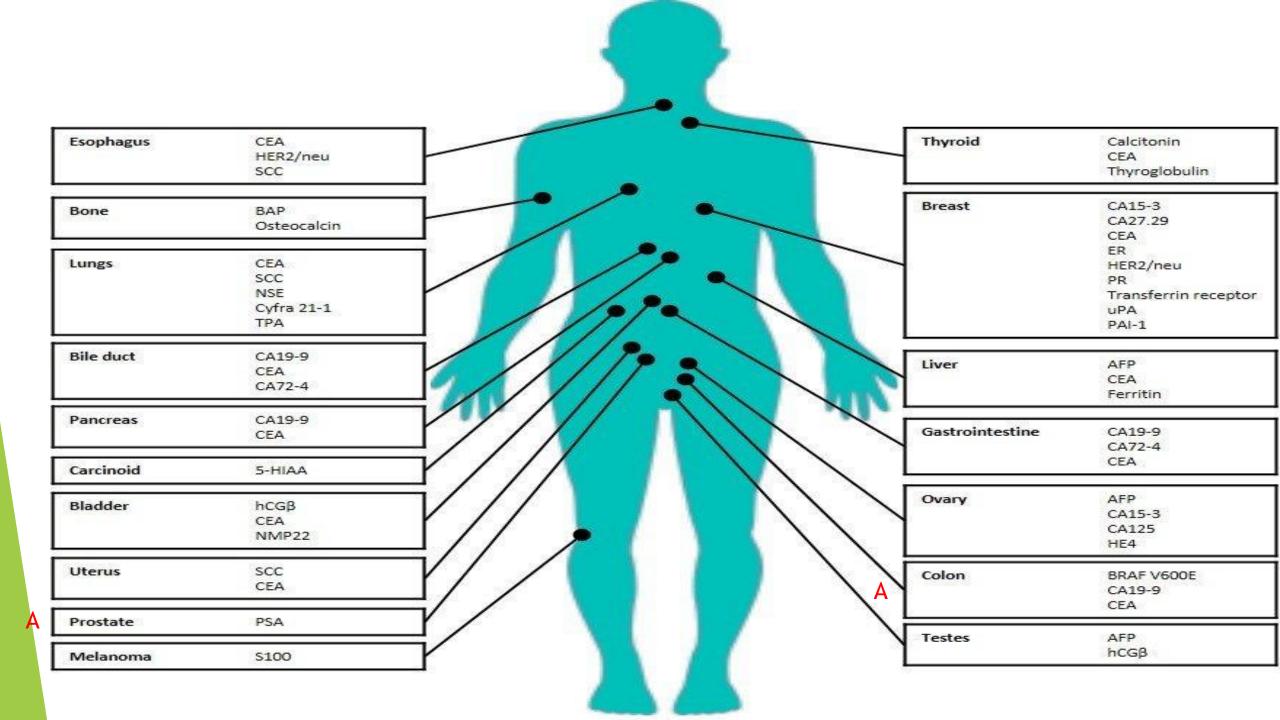
- Diagnosis of different pathologies, before structural changes, occur, since metabolic changes precede anatomical changes.
- Improved prognosis of many diseases by allowing an early diagnosis.
- It is possible to assess early response to therapy in the patient through variations in the metabolism of an injury.
- Reduce costs by avoiding unnecessary procedures, treatments, and hospitalizations.
- It can replace multiple diagnostic procedures.
- It also identifies lesions of a distant metastasis type that will change the therapeutic behavior.

Cost-effectiveness between tumor marker and PET/CT scan: about 100 times difference

- ► CEA: 400 PSA:400
- ► CA199:400
- PET/CT:36500~40000
- From cost-effectiveness points of view, if CEA and CA199 really are good lab
- ► follow up tools, how could PET/CT becomes a follow up tool? So expensive?
- Overall sensitivity of tumor marker and PET/CT: 60% VS 90%.
- Specificity:? 60% vs 95%?
- ▶ CTC ;Circulating Tumor Cell 循環腫瘤細胞液態切片檢測
- ▶ 本法為全球目前最新檢測技術 費用大約落在5000-20000左右
- ▶ NGS technology: next generation sequence of tumor gene analysis.NT:38500
- ▶ 1 cm mass in tumor number is 1 billion and PET/CT high resolution is 0.5 cm.

Breast cancer Lung cancer Colorectal cancer Pancreas cancer Prostate cancer HCC Ovarian cancer Thyroid cancer

	Туре	Marker	Half-life	Cancer or other
	Hormone	Calcitonin	12 min	Thyroid medullary carcinoma
		eta -HCG	18~24 hr	Germ cell tumor or GTD*
	Tumor associated protein	PSA	2~3 days	Prostate cancer, BPH, prostatitis
		CA125	4~5 days	Ovarian cancer, menses, peritonitis
		CA153	<2 weeks	Breast cancer
		CA199	14 hr	Pancreatic cancer, pancreatitis
	Oncofetal antigen	lpha -fetoprotein	3~6 days	Hepatic carcinoma, testis cancer,
				cirrhosis, hepatitis
		CEA	2 weeks	Adeno^, smoking, bronchitis
	Other	eta -microglobulin	80 min	MM, MGUS" , infection
		Thyroglobulin	weeks	Thyroid follicular carcinoma



Tumor marker is not diagnostic: for attention and alert

Imaging study is diagnostic(very important)

Medical evidence(PETCT) is seeing is believing.

In recurrent colon cancer:

tumor marker>traditional scans>PET/CT scan.

In fresh prostate cancer:

Tumor marker>perianal sonography or Biospy combined with traditional scan, PSMA PET, NaF PET better than WBBS for bone meta.

Tumor marker kinetics: Tumor marker kinetics: Better than imaging to assess response to chemotherapy? Journal of Clinical Oncology > List of Issues > Volume 26, Issue 15_suppl >

CASE 1: recent biopsy proved P.C with high PSA level.

Due to GU doctor opinion: high PSA means high bone metastasis possibility for DDx bone meta.

Both scans show no evidence of Bone meta. NaF PET more sensitive?>1/3

What's your judgement & interpretation?

How to evaluate and reconsider pt like this? Triple assessment?







PSA in the blood is measured in units called nanograms per milliliter (ng/mL). The chance of having prostate cancer goes up as the PSA level goes up, but there is no set cutoff point that can tell for sure if a man does or doesn't have prostate cancer. Many doctors use a PSA cutoff point of 4 ng/mL or higher when deciding if a man might need further testing, while others might recommend it starting at a lower level, such as 2.5 or 3.

- Most men without prostate cancer have PSA levels under 4 ng/mL of blood. Still, a level below 4 is not a guarantee that a man doesn't have cancer.
- Men with a PSA level between 4 and 10 (often called the "borderline range") have about a 1 in 4 chance of having prostate cancer.
- If the PSA is more than 10, the chance of having prostate cancer is over 50%.

prostate cancer is over 50%.

If your PSA level is high, you might need further tests to look for prostate cancer.

To learn more about how the PSA test is used to look for cancer, including factors that can affect PSA levels, special types of PSA tests, and what the next steps might be if you have an abnormal PSA level, see Screening Tests for Prostate Cancer.

Results: Patients with bone metastases demonstrated a median serum PSA GU DOCTOR HIGH BELIEVE. concentration of 151 ng/ml and only 1 patient revealed a serum PSA concentration of < 10 ng/ml. This resulted in a negative predictive value of 98%. In addition 67% of these patients demonstrated a serum PSA concentration of > 100 ng/ml, which resulted in a positive predictive value of 74% and an overall accuracy of 92%. Urol Int 1996;56:169-173

1101118 PSA 124 1110316 PSA 135 1110703 PSA 68.1 1110801 PSA 2.2

TRIPLE ASSESSMENT IN BONE METASTASIS

Gleason's score: 4+5=9 adenoCA

CT of abdomen: no LNs,T2cN0M0,stage

How many chance of this case bone metastasis?

WHAT'S ORDERING NaF cutoff value of PSA? New case:>20 ng/ml; old treatment case:>6 ng/ml. WJNM 2018

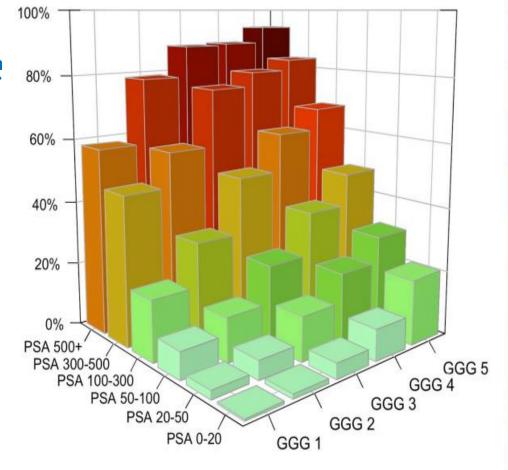
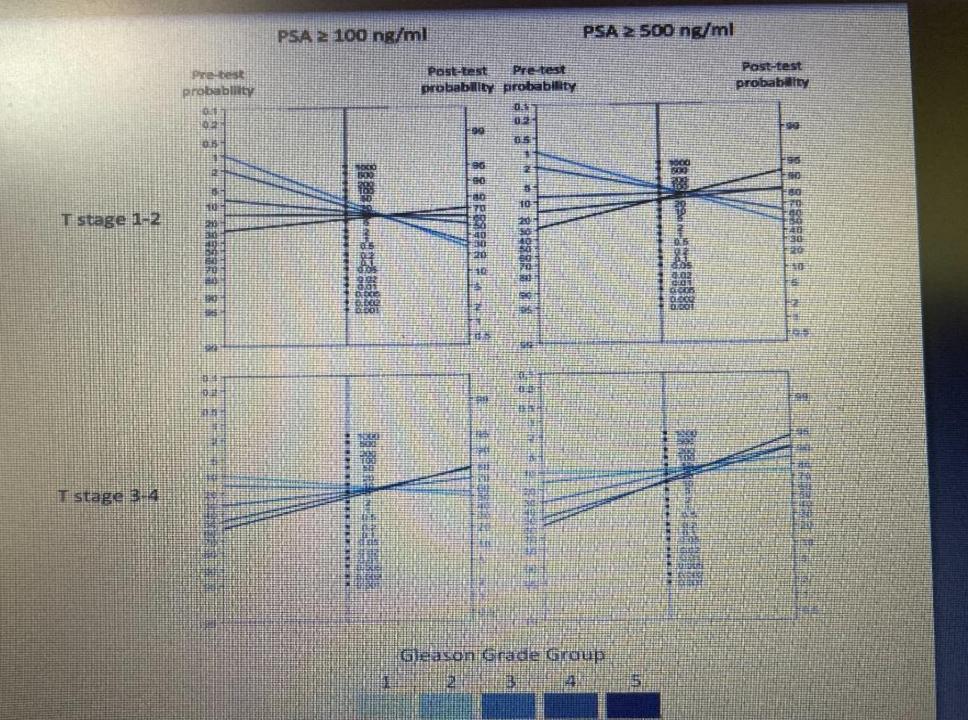


Fig 1. Proportion and number of men with metastases stratified by prostate-specific antigen



Gleason's Pattern Scale

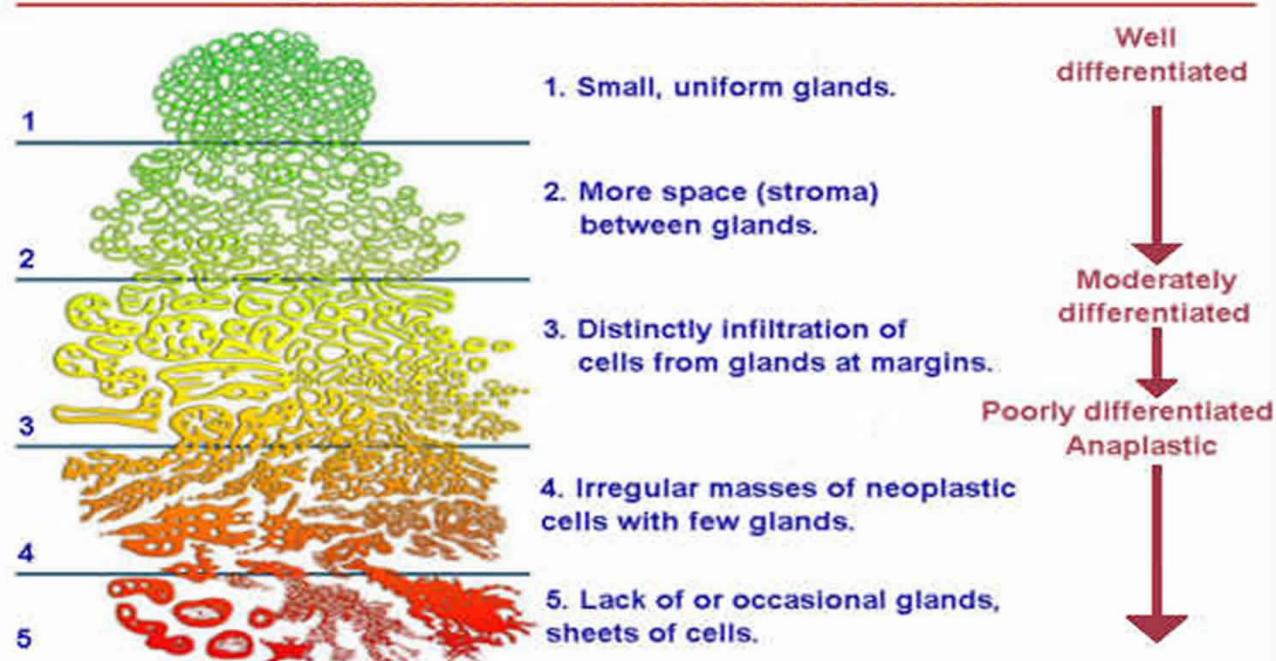
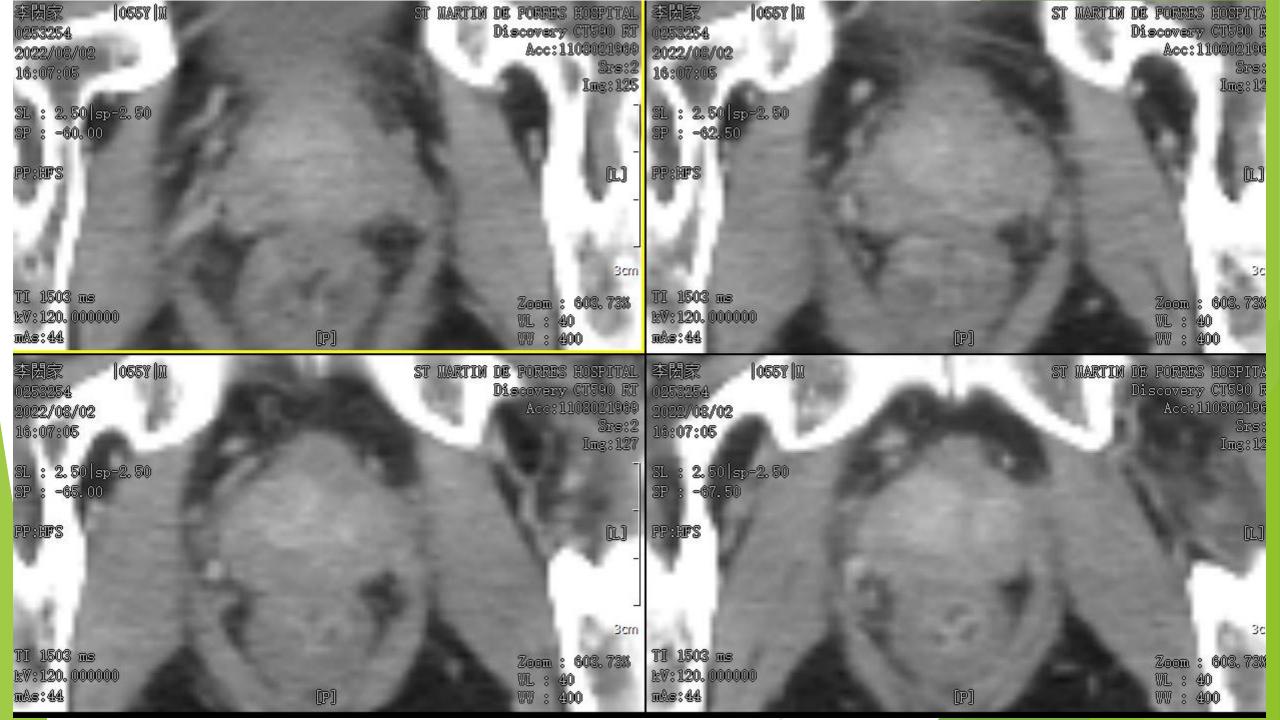


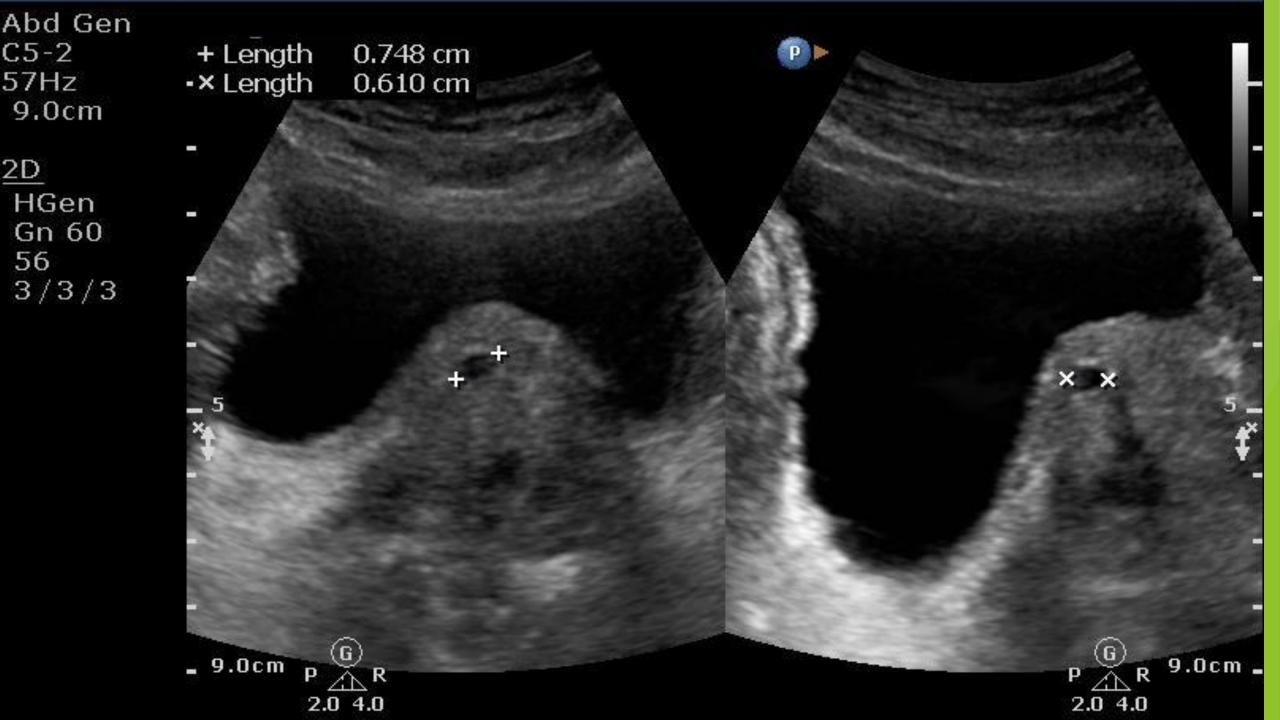
Table 5: Correlation between 2005 & 2014 grading

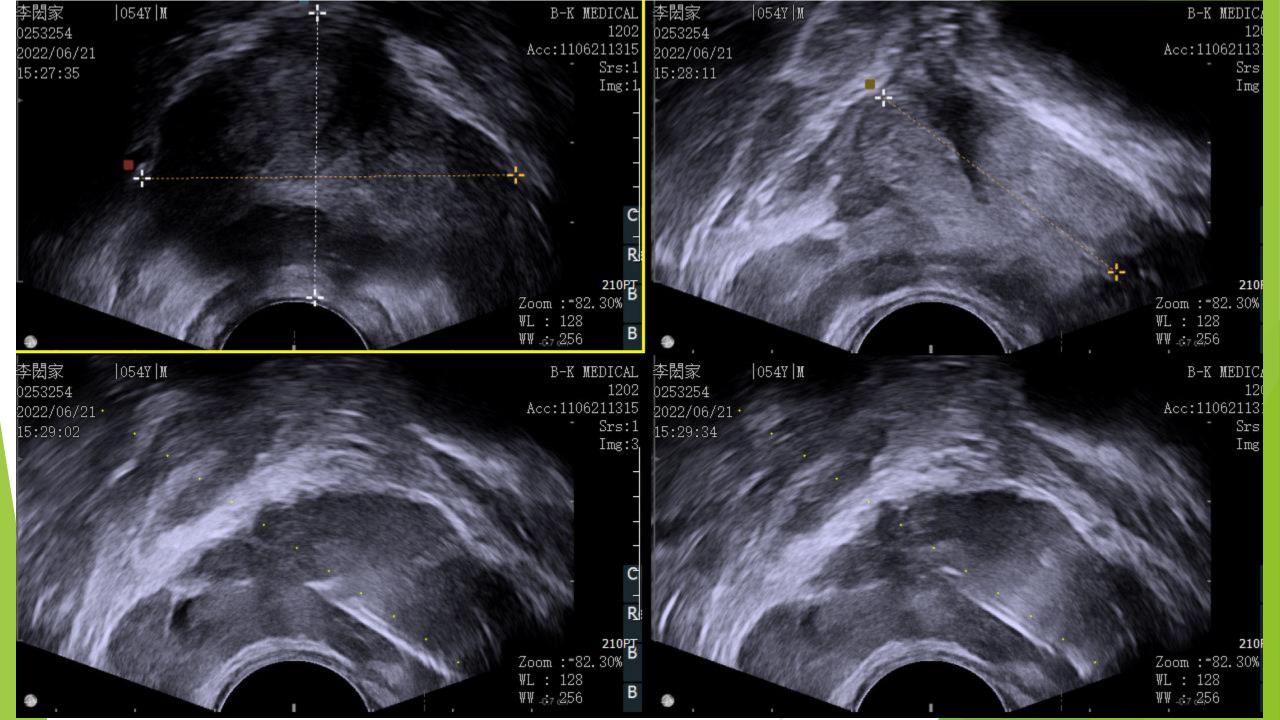
Gleason score (2005)	No. of cases	Gleason grade group (2014)
< 6	10	GGG 1
3+4=7	14	GGG 2
4+3=7	6	GGG 3
4+4, 5+3	2	GGG 4
9-10	6	GGG 5
No Grading*	3	GG1: 2 GG3: 1

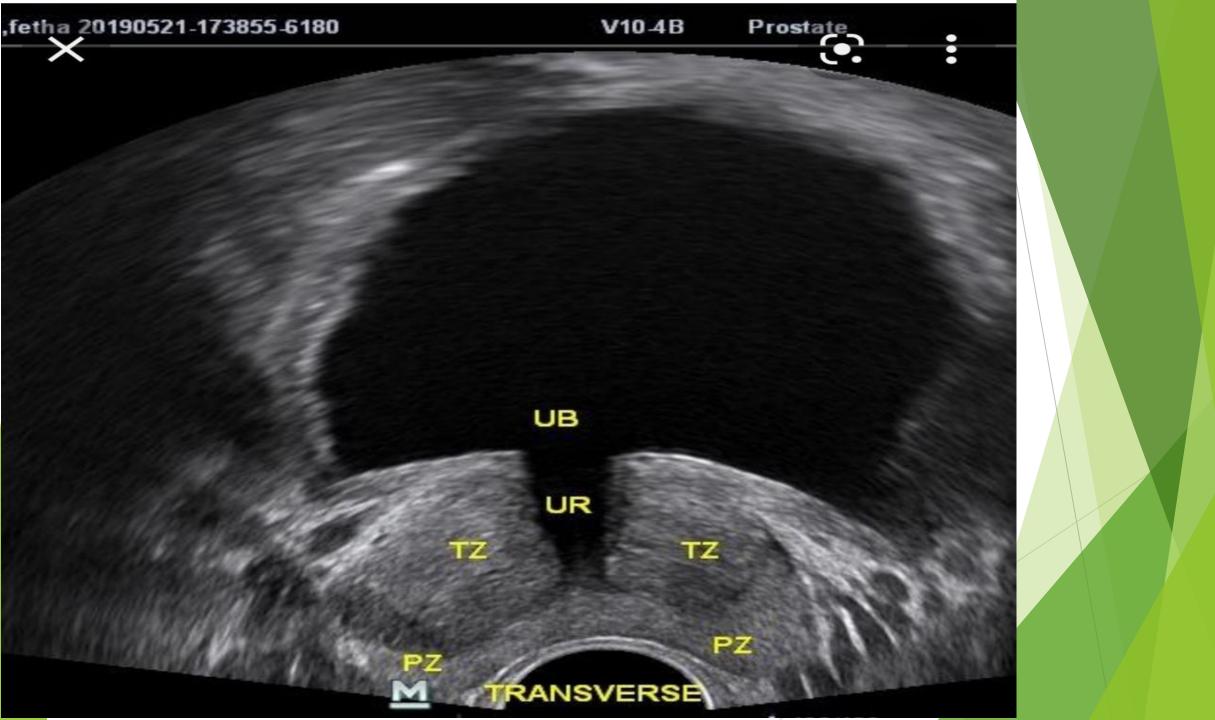
Recently the Gleason system has been compressed into so-called grade groups (GGG). The new GG system was validated in two large cohorts (men treated with radical prostatectomy (RP) or radiation), and both studies discovered that GGs predicted the risk of recurrence following the primary treatment [1, 2]. In the larger study, the five-year biochemical recurrence (BCR)-free progression probabilities after RP for GGs 1 through 5 were 96% (95% confidence interval (CI), 95-96), 88% (95% CI, 85-89), 63% (95% CI, 61-65), 48% (95% CI, 44-52), and 26% (95% CI, 23-30), respectively [1].

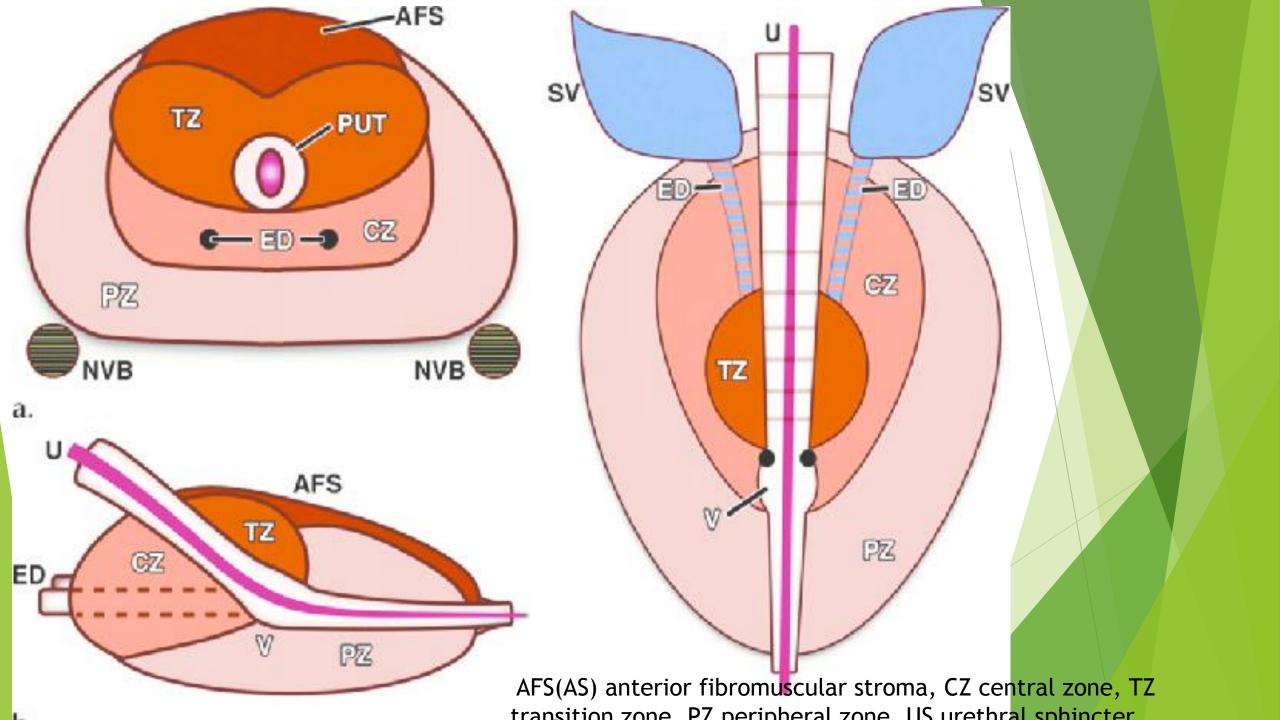












- 73.前列腺癌最常發生於前列腺的下列何區?
- (A)中央區 (central zone)
- (B)移形區(transitional zone)
- (C)尖端區 (apex)
- (D) 周圍區 (peripheral zone)

編輯私有筆記及自訂標籤

臨床生理學與病理學- 105 年 - 105-2 專技高考_醫事檢驗師: 臨床生理學與病理 #5478

答案:D

難度: 適中

討論

→私人筆記(0)

最佳解!

小魚兒 國一下 (2016/11/21)

前列腺可分下列幾個重要部份: 1. 移形區: 為良性前列腺肥大好發之部位2. 周邊

區:為前列腺.....觀看完整全文,請先登入

檢舉

大業哥哥 (2022/02/07)

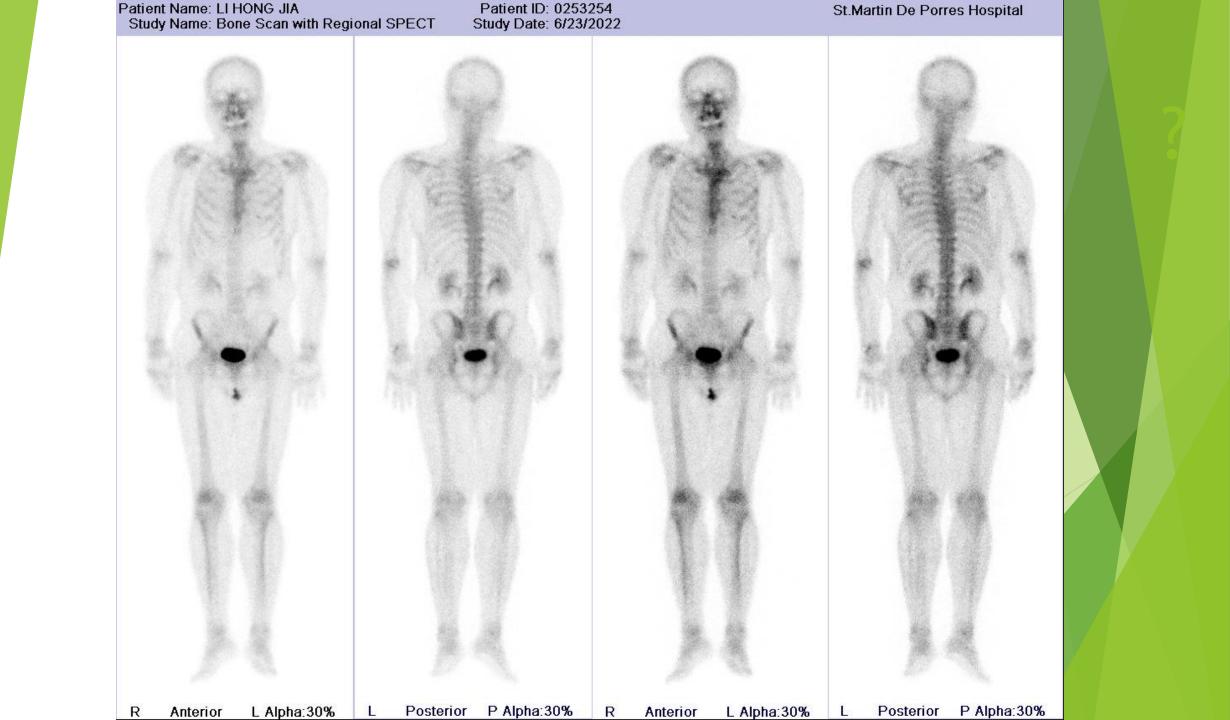
補充:106-1

良性前列腺肥大(benign prostatic hypertrophy),最常發生於前列腺的那個區域

移形區(transitional zone)

学

21







TRUS biopsy(6/21):3.6*4.6*3.6 cm3 about 32.6 cc prostate. Hypoechoic lesions over bilateral lobe: Rt>Lf

Abd CT(6/21):right prostate ca confied in prostate Without other lesion. Stage I T2aN0M0.

Due to negative bone metastasis proved by bone scan Even NaF PET, EBRT for this patient is performed 2 ms.

Reason of high PSA to normal PSA:

EBRT(external beam radiotherapy):high dose RT. PSA change to be normal. also decreased in testosterone dosage with routine use(3.38 ng/Ml)

領血紀錄 | Covid 19檢驗 | 阿里山醫療站POCT | F2=生化檢驗 | F1=血液檢驗 <mark>F9=肝炎血清&腫瘤標誌</mark>| F7=血清免疫檢驗 | F5=CKD | F6=內分泌 | F8=代謝 | F11=肝炎HCV | F10=肝炎HBV | F4=TB抗酸菌報告彙 報告日期 | 時間 | 門急住 HBsAg Anti-HBs | HBeAg |Anti-HBe |Anti-HBc |AFP |PIVKA-II |HCV-Ab 111/08/31 14:58 0 111/08/05 14:48 0 Reactive(1095.00) Non-reactive(0.10) Non-reactive(0.04) 111/08/01 15:14 0 111/07/05 14:58 0 111/06/10 10:10 0 2.2 111/03/16 11:04 0 135.0 110/11/17 10:39 0 124.0 109/11/04 10:46 0 Non-reactive(0.03) Reactive(1521.00)

If bone metastasis, Ra-223 could be suggested.

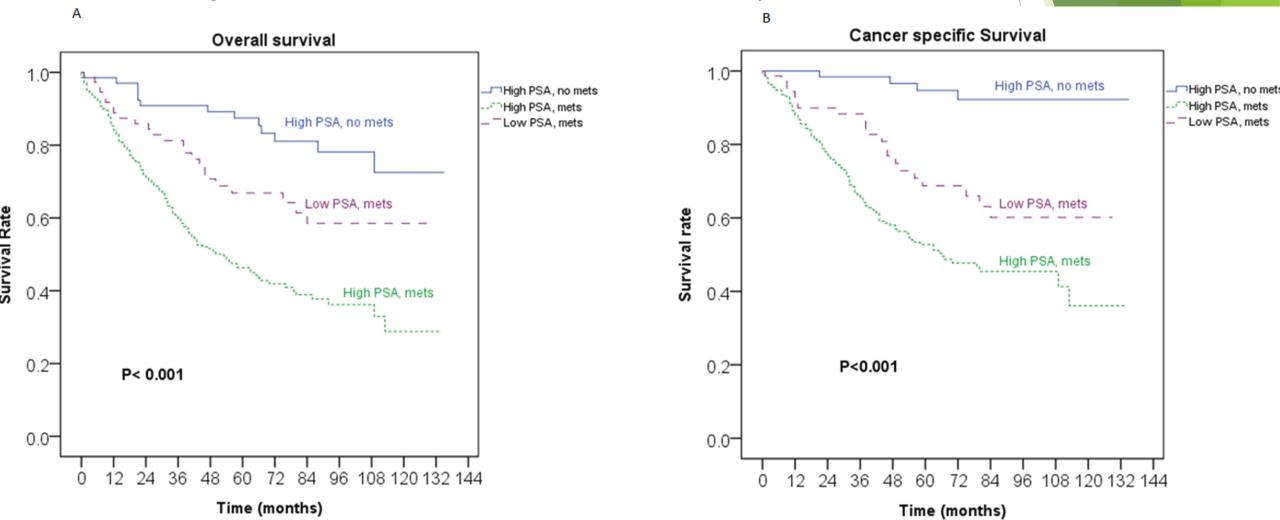
Radium-223, a radioactive substance, is used to treat men with metastatic prostate cancer that no longer responds to hormone therapy. Because it mimics calcium, the radium is selectively absorbed into areas where prostate cancer is invading bone. This revolutionary treatment has been shown to improve the survival of men with metastatic prostate cancer that has spread to the bones, and to delay problems in the bone such as pain or fracture.

Reason of PSA return to normal of this patient

Radiotherapy only and no other possibility like 7 reasons for non malignacy. Pure cancer treatment

ABOUT THIS CASE:50s with high PSA OVER 100 ng/Ml and well Response after RT. Why so good in this group of patient?

Patient with high PSA value were not destined to have metastatic PC. Non-metastatic patients With a high PSA level obtained a survival benefit from local prostate-definitive treatments.



FALSE POSITIVE REASONS in high PSA:

- 1.FOLLY
- 2.BPH
- 3. Prostatitis
- 4. Ejaculation before study
- 5.UTI before study
- 6.Bladder endoscopy and ureteroscope
- 7. Riding bicycle or riding horse before study
- 8. Trauma before study
- 9.Age

359 prostate cancer patients with (n = 40) and without (n = 319) bone metastases were analyzed. In all patients the initial PSA measurement as well as the radionuclide bone scan were evaluated.

Results: Patients without bone metastases demonstrated a median serum PSA concentration of 12 ng/ml, whereas those with bone metastases revealed a median serum PSA concentration of 59 ng/ml, with 7 patients demonstrating a serum PSA concentration of < 10 ng/ml. This resulted in a negative predictive value of 96%. In addition, only 40% of these patients with bone metastases demonstrated a serum PSA concentration of > 100 ng/ml, which resulted in a positive predictive value of 50%.

Conclusion: The serum PSA concentration seems only to <u>provide limited information</u> with regard to the presence of bone metastasis in patients with newly diagnosed cancer of the prostate. We therefore question whether a staging radionuclide bone scan may be omitted in patients with a serum PSA value of < 10 ng/ml.

Eur Urol 1998;33(4):376-81. doi 10.1159/000019619. Is prostate-specific antigen a reliable marker of bone metastasis in patients with newly diagnosed cancer of the prostate?

Sixty-two patients (32 newly diagnosed and 30 previously treated) met the inclusion criteria. Near half of previously treated patients were on hormone therapy. NaF PET/CT was positive in 9 newly diagnosed (PSA mean: 91.6 ng/ml, range: 6.2-226 ng/ml) and in 6 previously treated patients (PSA mean: 146.4 ng/ml, range: 6.6-675 ng/ml). ROC analysis indicated that PSA cutoff value for NaF PET/CT positivity was >20 ng/ml in newly diagnosed and >6 ng/ml in previously treated patients. PSA cutoff value for ordering NaF PET/CT in newly diagnosed patients does not seem significantly different than the previous results for BS (>20 ng/ml). However, we found a lower PSA cutoff value of >6 ng/ml tomography/computed tomography bone in previously treated patients.

World J Nucl Med. 2018 Oct-Dec; 17(4): 281-285.

Prostate-specific antigen cutoff value for ordering sodium fluoride positron emission scan in patients with prostate cancer

Materials and methods: In a retrospective study 158 prostate cancer patients with (n = 21) and without (n = 137) bone metastases were analyzed. In all patients the initial PSA measurement as well as the radionuclide bone scan were evaluated.

Results: Patients with bone metastases demonstrated a median serum PSA concentration of 151 ng/ml and only 1 patient revealed a serum PSA concentration of <10 ng/ml. This resulted in a negative predictive value of 98%. In addition 67% of these patients demonstrated a serum PSA concentration of >100 ng/ml, which resulted in a positive predictive value of 74% and an overall accuracy of 92%.

Conclusion: The serum PSA concentration seems to provide useful information with regard to the presence of bone metastasis in patients with newly diagnosed cancer of the prostate. A serum PSA value of <10 ng/ml nearly excludes bone metastases, whereas a serum PSA value of > 100 ng/ml is highly predictive of bone metastases.

WRONG PAPER? MAYBE MADE OF IT?

Urol Int

. 1996;56(3):169-73. doi: 10.1159/000282834. Prostate-specific antigen as a marker of bone metastasis in patients with prostate cancer

WHY SOME FRESH CASE OF P.C HAD NORMAL PSA BUT BONE METASTASIS?

According to the results of our study; the free PSA, total PSA, free PSA/total PSA ratio and Gleason score values were not considered as a reliable parameter in the prostate cancer cases follow-up for bone metastasis development. Only ALP had a diagnostic value and ALP cutoff value was 76.50 IU / L with 80% sensitivity and 82.1% specificity in predicting bone metastases in prostate cancer.

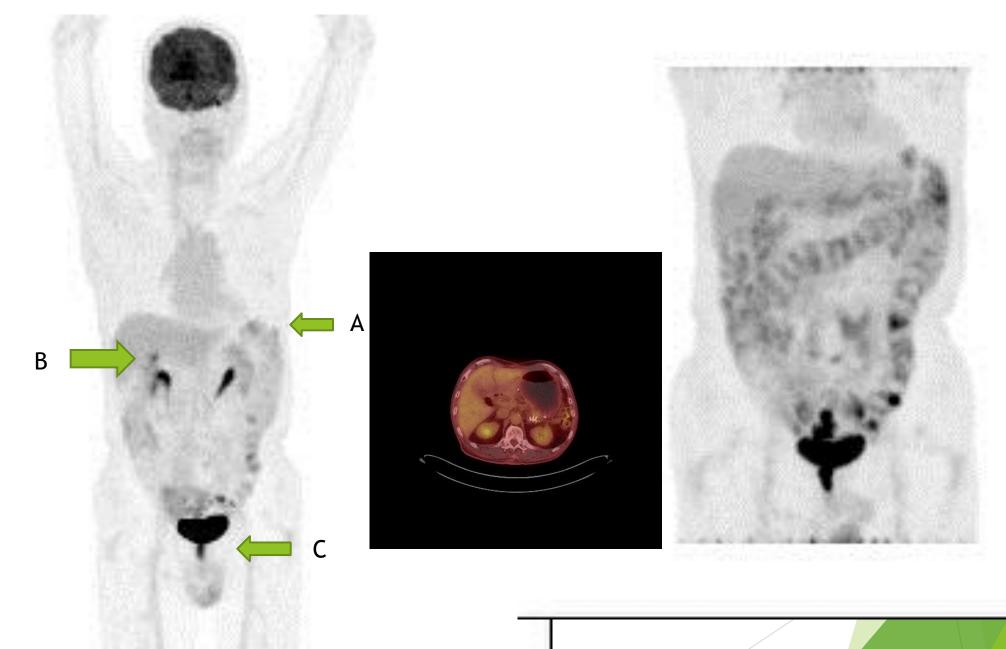
Case 2: colon cancer and pancreas cancer

Cancer Antigens (CEA and CA 19-9) as Markers of Advanced Stage of Colorectal Carcinoma Med Arch. 2013 Dec; 67(6): 397-401.

It is very difficult to convicted a criminal not guilty, especially many.

Why PET scan in recurrent colon cancer?

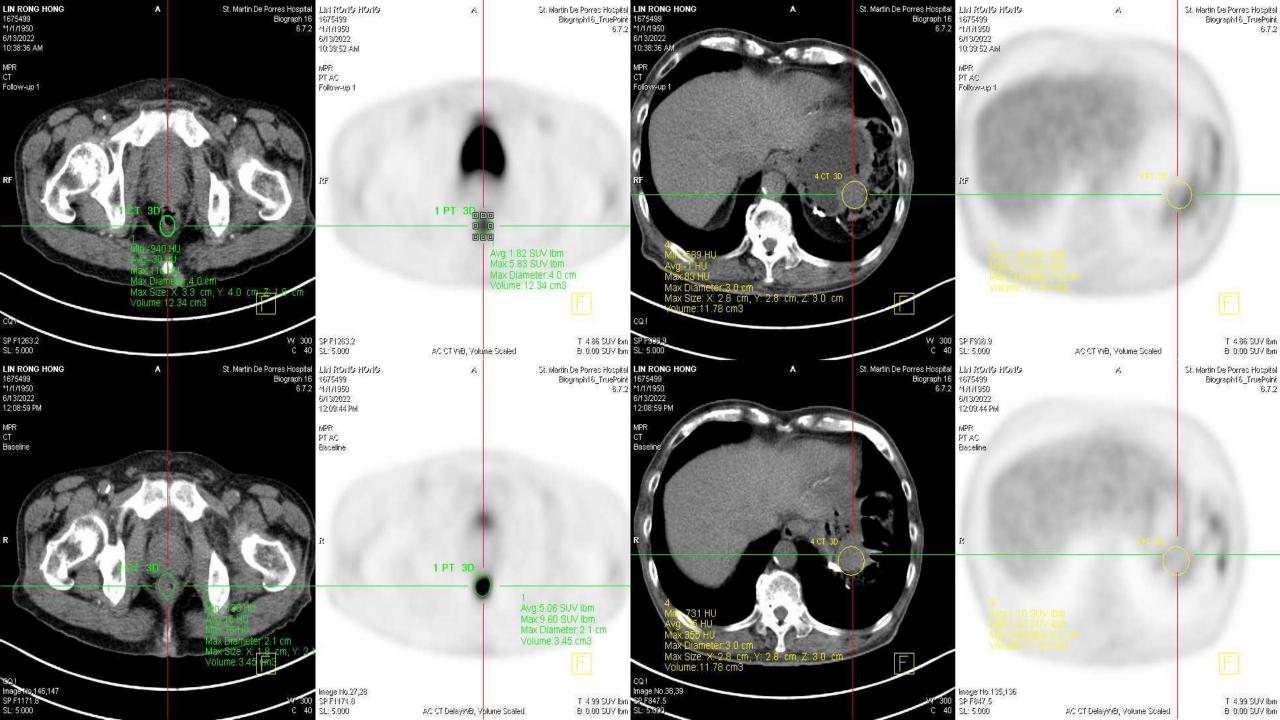
- ▶ 1. normal CEA: PET scan had 2/3 patient + 1/3 in electronic database review 85% of PPV and 61% of NPV in cases of recurrent CRC,2007.In recurrency 95%, extent of dis.
- In liver metastasis, PET scan as a good tool for suspected early recurrent CRC 88%. Also plan surgical or nonsurgical treatment(RT).
- ▶ 2.high CEA: Even more higher in PPV or NPV.

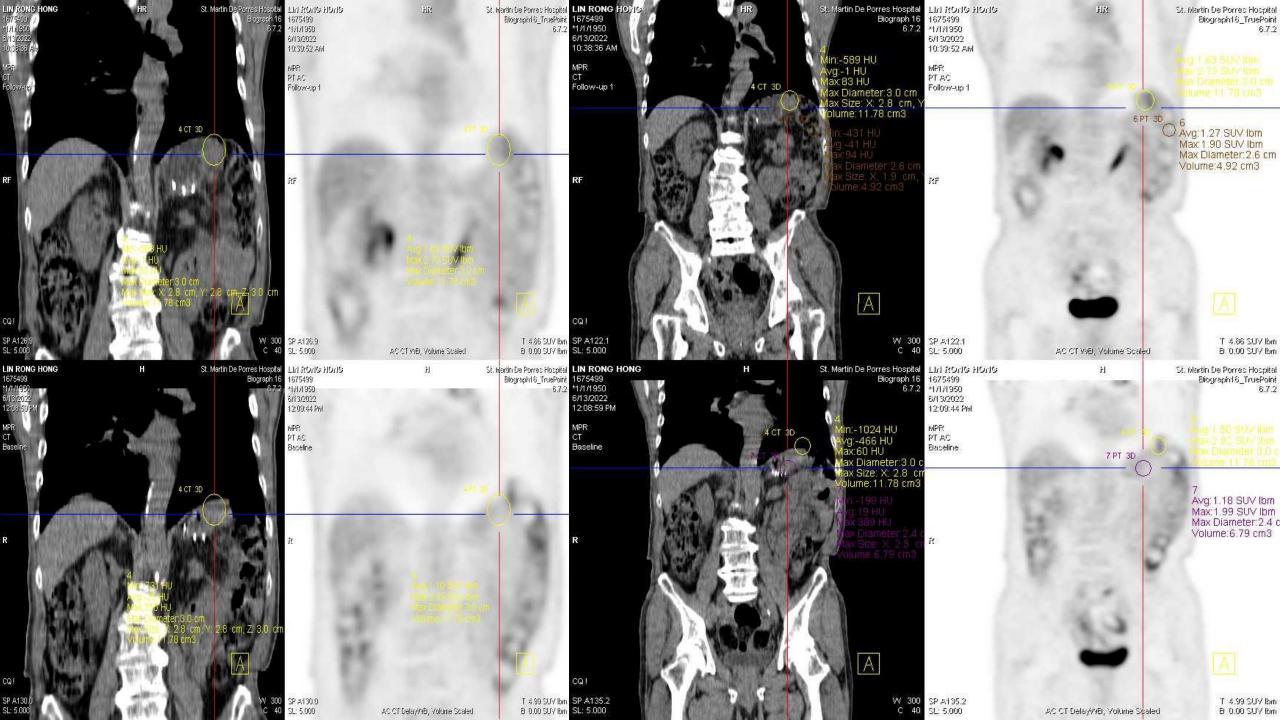


A:proved to be surgical effect near lung

B:may related to suprarenal or renal caliectasis

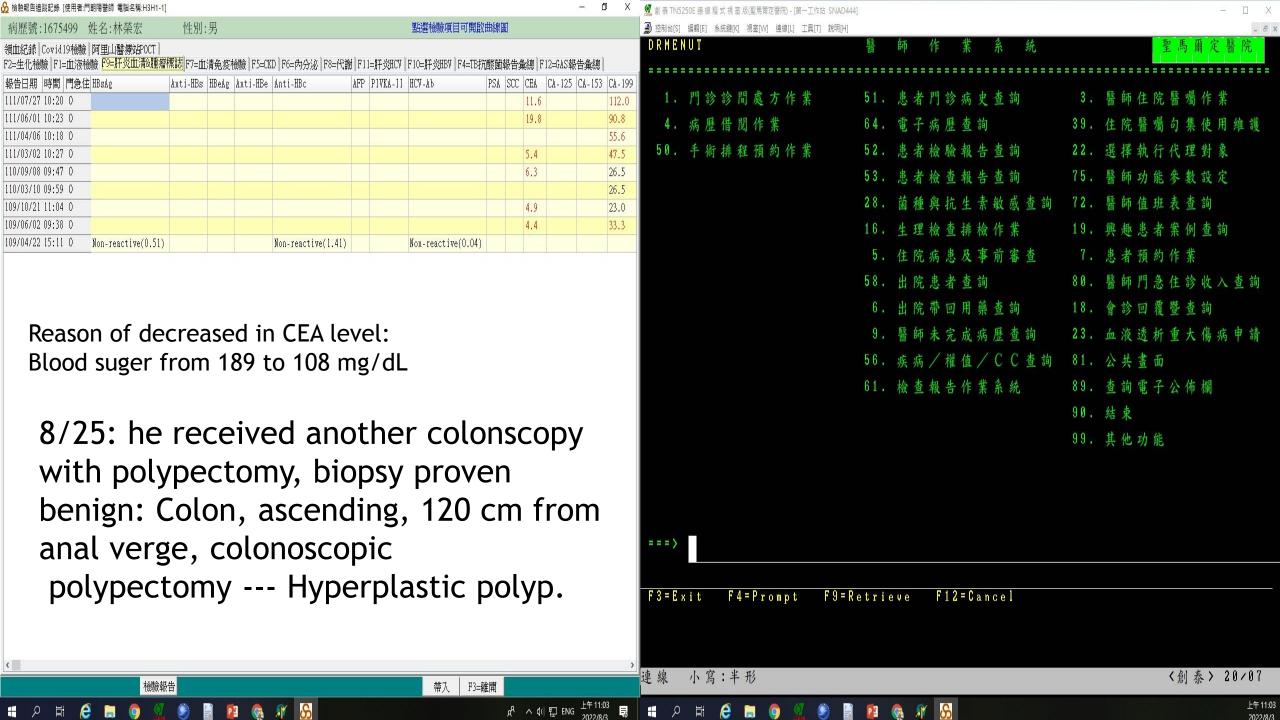
C:Anal lesion:anosocpy proved to be hemorrhoid.





Efficiency of the combination of 18F-FDG PET/CT, CEA, and CA199 in detection of colorectal cancer and monitoring postoperative tumor metastasis. Int J Clin Exp Med 2018

SUV≥2.5 was adjudicated as the presence of malignant tumor. Serum CEA>3.4 ng/mL and CA199>27 U/mL were adjudicated as positive CRC results. In the combined detection by 18F-FDG PET/CT, CEA, and CA199, SUV equal to or greater than 2.5 and positivity of CEA and CA199 were defined as presence of a malignant tumor. The diagnostic efficiency of combining 18F-FDG PET-CT, CEA, and CA199 in detecting CRC and its value in monitoring tumor metastasis were analyzed. Results: The results of SUV, CEA, and CA199 in CRC patients were remarkably higher than those in normal volunteers (all P<0.001).SUV, CEA, and CA199 were highly expressed in patients. Accuracy of the three-modality combination in detection of CRC was 92.23%, sensitivity was 96.87%, and specificity was 87.00%, which were superior to those of the single modality (P<0.05). Moreover, the three-modality combination had high sensitivity and specificity for monitoring postoperative metastasis of tumors. Conclusion: Combination of 18F-FDG PET-CT, CEA, and CA199 in the diagnosis of CRC has higher accuracy, sensitivity, and specificity, and it was effective in monitoring postoperative metastasis of CRC in patients. Thus, it is worthy of extensive clinical use.



Reasons for CEA increased in nonmalignant disease:

cigarette smoking, pancreatitis, biliary obstruction, peptic ulcer disease, and hypothyroidism, but the extent of elevation is substantially less, and it is rare to see an elevation of >10 ng/ml in this context.

Common causes for an elevated (CEA) level: Colorectal Cancer Primary ovarian cancer Breast cancer Thyroid cancer Non-small cell lung cancer Cigarette smoking Mucinous cystadenoma of ovary/appendix Cholecystitis Liver cirrhosis **Pancreatitis** Inflammatory bowel disease Medications like orlistat

False-positive elevated CEA during colon cancer surveillance: a cholecystitis case report diagnosed by PET-CT scan Journal of Surgical Case Reports, Volume 2019, Issue 6, June 2019, 138,

A 53-year-old man with previous history of sigmoid colon adenocarcinoma who had undergone surgical resection and adjuvant chemotherapy presented with slightly rising carcinoembryonic antigen (CEA), while anatomical imaging modalities were unremarkable. FDG PET-CT study did not identify residual tumoral disease; however, there were abnormalities in the gallbladder most likely suggestive of cholecystitis. Eight weeks after cholecystectomy, serum CEA concentration reached normal values. Final histopathology of the gallbladder was also consistent with acute on chronic cholecystitis.

Carbohydrate antigen 19-9 elevation without evidence of malignant or pancreatobiliary diseases
Scientific Reports volume 10, Article number: 8820 (2020) Cite this article

Etiologic diseases	No. of subjects
Hepatic diseases	63 (32.8%)
Pulmonary diseases	32 (16.7%)
Gynecologic diseases	38 (19.8%)
Endocrine diseases	13 (6.8%)
Spleen cyst	1 (0.5%)
Unknown cause	45 (23.4%)

Gut. 2003 Jun; 52(6): 913-914. A new cause for CA19.9 elevation: heavy tea consumption

Laboratory data demonstrated were negative. Serum CA19.9 was 1432 UI/ml (normal <37), and CEA was 2 ng/ml(normal <5).

Upper endoscopy, colonoscopy, and barium study of the small bowel showed normal results. Abdominal ultrasonography and computed tomography scan showed no pancreatic malignancy or biliary abnormalities. The pancreas was homogenous and mildly enlarged in the body without pathological significance.

Spirometry, chest x ray, bronchoscopy, and bronchoalveolar lavage fluid examination were normal.

The patient was advised to stop tea consumption. Four weeks later she became symptom free and gained the 2 kg weight loss. Another serum CA19.9 assay showed a considerable drop in levels to 42 UI/ml. A rechallenge test was then attempted. The patient restarted tea consumption as previously. Four weeks later CA19.9 increased to 745 UI/ml followed by a fall to 25 UI/ml one month after withdrawal. Follow up one year later revealed no clinical abnormalities. Abdominal and chest computed tomography scan were normal.

Clin Colorectal Cancer 2020 Dec;19(4):e200-e207. Carcinoembryonic Antigen-related Tumor Kinetics After Eight Weeks of Chemotherapy is Independently Associated With Overall Survival in Patients With Metastatic Colorectal Cancer

After 8 weeks from the beginning of chemotherapy, CEA reduction rate of 50% and CEA-specific growth lower than - 0.5%/day are effective prognostic factors among patients with high serum CEA levels and could become useful intermediate endpoints of clinical trials.

New tumor marker: CTC(circulating tumor cells):

particularly valuable for treatment monitoring in patients that have disease that cannot be evaluated by radiology.

CTC count by the CellSearch® system is a validated prognostic factor at baseline, but is also used for treatment monitoring

Value of CT, FDG PET-CT and serum tumor markers in staging recurrent colorectal cancer

155 patients (87 men, mean age: 61 years) remained for final analysis. Serum CEA and CA 19-9 had a sensitivity of 74 and 35% and specificity of 86 and 83% for the detection recurrent CRC, respectively. The sensitivities of CT and FDG PET-CT were 79 and 92% and specificities were 45 and 100%, respectively. At an adaptive threshold of 42%, the median SUVmax, SUVmean, MTV and TLG of these lesions were 8.8, 5.2, 11.3 cm[Formula: see text] and 55.4, respectively. All FDG PET-CT quantitative parameters correlated positively with serum CEA levels, and the correlation coefficients were 0.45, 0.44 and 0.49 for SUVmax, MTV and TLG [Formula: see text].

Conclusion: PET-CT scan, CEA and CA-19-9 results were correlated. However, both tumor markers had poor sensitivity to detect metastatic disease. PET-CT is more accurate than CT in detecting recurrent CRC in this study. Majority of the recurrences were in the liver and the sensitivity is affected by tumor histology. The correlation between semiquantitative FDG PET parameters and serum tumor marker levels is moderate.

Int J Comput Assist Radiol Surg. 2015 Jul;10(7):993-1002

Conclusion:

- 1.TUMOR MARKER IS NOT DIAGNOSIS AND JUST FOR SCREENING/MONITORING.
- 2.PET/CT scan is diagnostic and needs other lab data for increased S/Sp.
- 3. We need to know tumor marker false positive condition of malignat & nonmalig.
- 4. History asking is important, can eliminate unnecessary study like PET?
- 5. Tumor marker kinetics could be assessed to judge tumor recurrent or not.

Tumor marker result may inteferred by many factor including patient himself or?