EBM 月會

Evidence-Based Medicine

Reporter: R1 丁楷庭

DATE: 101/03/05

Clinical scenario-1

- A 61 year-old female patient
- Operation History:
  left thigh lipoma status post excision 10+ years ago at YUAN'S General Hospital(阮綜合)

Clinical scenario-2

According to herself:

- insidious onset of left thigh mass with enlargement for 10+ years
- This mass was noted 3-4 years after excision
  → the mass progressively enlarged
- Associated symptom/sign:
  pain(-), tenderness(-), general malaise(-), weight loss(-)

Clinical scenario-3

- Due to problem above, she came to our OPD
  →MRI revealed:
  a fatty mass lesion (8.0cm x 4.1cm x 18.8cm) with moderated enhanced soft tissue component in the left rectus femoris. Favor malignant lesion.
  Highly consider liposarcoma.
  DDx: other fat contanied lesion.
- Therefore, she was admitted to our ward for further management at 2010/4/27.

Clinical scenario-4

- Past History:
  - Hypertension: denied
  - Diabetes Mellitus: denied
  - Other systemic disease: denied
- Operation history:
  left thigh lipoma status post excision 10+ years ago at YUAN'S General Hospital(阮綜合)
- Personal, Social and Occupational History:
  - Cigarette Smoking : denied
  - Alcohol : denied
  - Occupation history : unremarkable
  - Contact history : unremarkable
  - Travel history : denied

Clinical scenario-5

- Current Medicine
  - denied
- Allergy History
  - denied

Clinical scenario-6

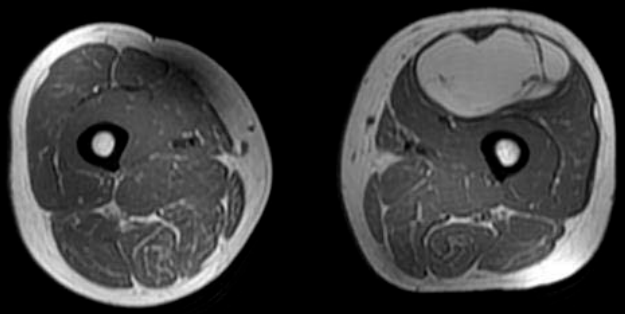
- Physical Examination
  - Vital signs: BP: 137/79 mmHg PR: 69 bpm
    RR: 20 cpm BT: 37.2 ℃
  - consciousness: clear
  - conjunctiva: not pale
  - Chest: symmetric expansion
    breathing sound: bilateral clear
    heart sound: regular heart beat,
    murmur (-)
  - Abdomen: soft, mild distended
    bowel sound: normative
  - Extremities: freely movable, no pitting edema

Clinical scenario-7

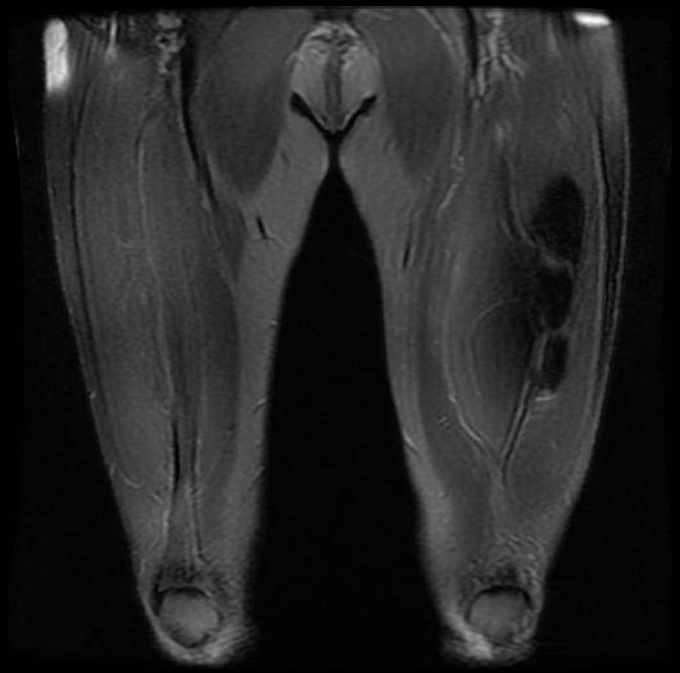
- Local finding:
  an elastic soft mass
  - about 10cmx15cm over anterior aspect of left thigh
  - movable
  - mild local heat
  - no tenderness
  - no redness

Clinical scenario-8

- MRI of Left Thigh:



T1 axial



T2 coronal

Clinical scenario-9

- Tentative Diagnosis or Impression:
  - left thigh soft tissue tumor
    R/O liposarcoma
- Plan :
  - tumor excision

Clinical scenario-10

- Pathologic diagnosis:
  - Soft tissue, thigh, left, wide excision, well-differentiated liposarcoma.
  - Microscopic Examination:
    - It shows a relatively well-defined tumor composed of adipocytic tissue with significant variation in cell size.
    - Focal adipocytic nuclear atypia is noted.
    - These neoplastic cells are positive for S-100 protein and MDM2.

提出background question -以what, when, who, where, which, how為字根的問題

- How to diagnose well-differentiated liposarcoma?

Well-differentiated liposarcoma

- Lipoma-like
- Well-circumscribed, lobulated masses
- Large, indistinguishable from benign lipomas grossly
- Relatively mature adipocytic proliferation
- Focal nuclear atypia, hyperchromasia
- Scattered hyperchromatic and multinucleated stromal cells may be present
- Varying number of *monovacuolated* or *multivacuolated lipoblasts* may be present

Well-differentiated liposarcoma

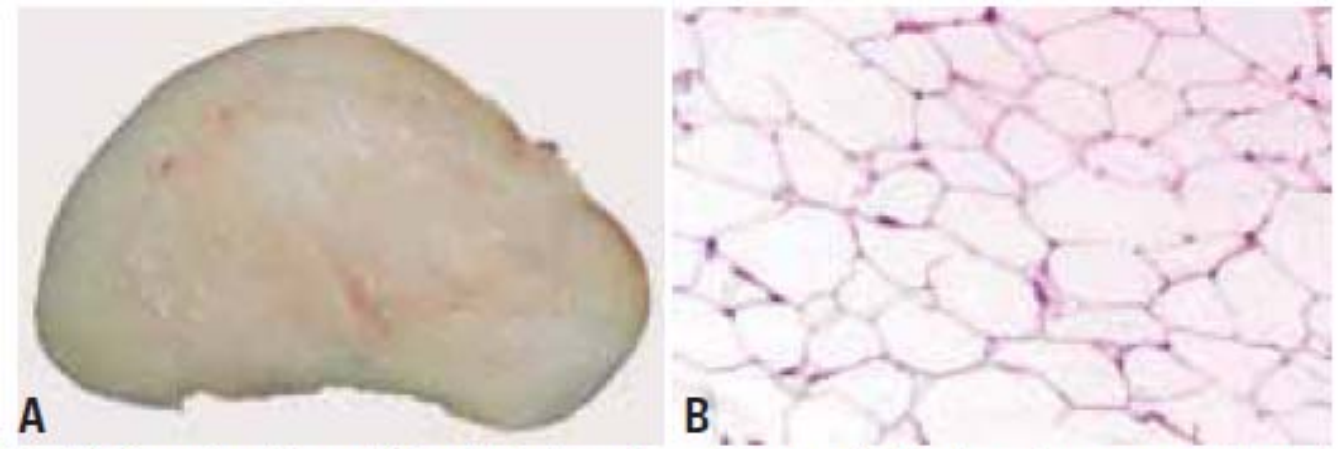


Fig. 1.03 Conventional lipoma. **A** Grossly, the tumour is well circumscribed and has a homogenous yellow cut surface. **B** The mature adipocytes vary only slightly in size and shape and have small eccentric nuclei.

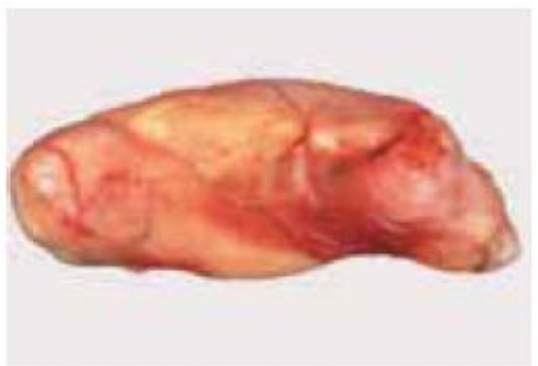
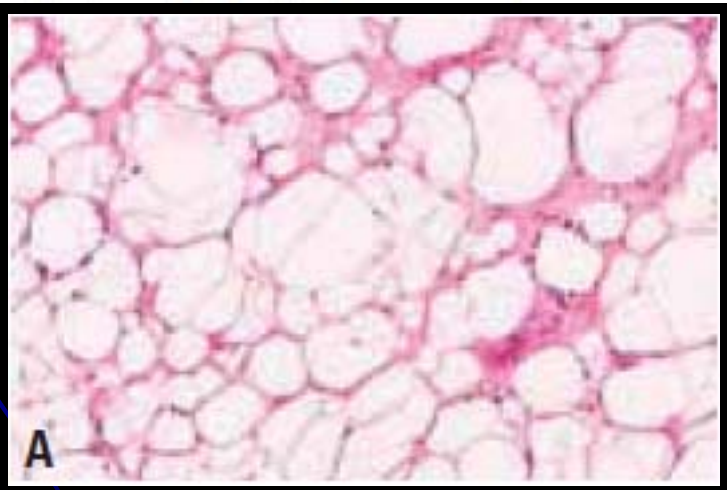
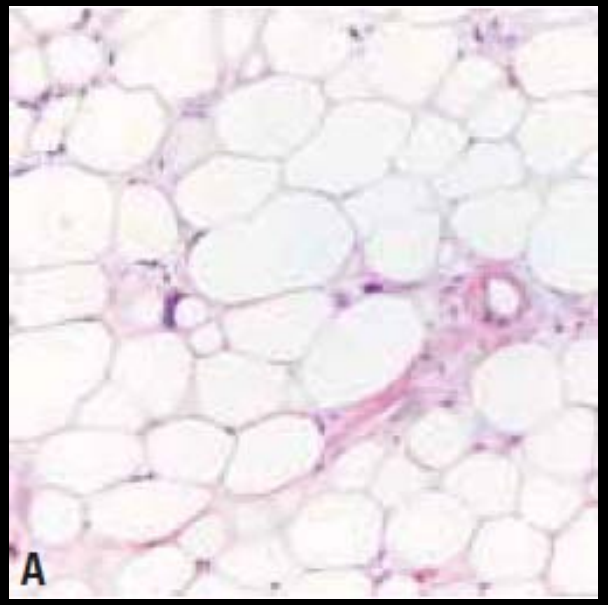


Fig. 1.29 Atypical lipomatous tumour / Well differentiated liposarcoma. Surgical specimen showing a well circumscribed, lobulated mass.





- 圖片出處：World Health Organization Classification of Tumours
  Pathology and Genetics of Tumours of Soft Tissue and Bone
  IARCPress Lyon, 2002

Well-differentiated liposarcoma

- Cytogenetically, well-differentiated liposarcoma harbor supernumerary ring and/or giant chromosomes, comprising amplicons of the 12q13-15 region that result in amplification of several genes including MDM2 and CDK4, HMGA2, and CPM.
- MDM2 and CDK4 are both consistently amplified and expressed. → The resulting overexpressed proteins can be detected immunohistochemically.

Well-differentiated liposarcoma

- Demonstration of MDM2 or CDK4 overexpression of proteins immunohistochemically
  → may be of help in distinguishing well-differented liposarcoma from lipoma.
- S-100 protein is focally but consistently found immunohistochemically in the cells of both benign and malignant adipose tissue tumors.

提出 Foreground question

- Is there a better diagnostic tool for differentiating well-differentiated liposarcoma and benign lipomatous tumor?

PICO

Q: Is there a better diagnostic tool for differentiating well-differentiated liposarcoma and benign lipomatous tumor?

P: Differentiating well-differentiated liposaroma and benign lipomatous tumor

I: better diagnostic tool (IHC)

C: MDM2

O: sensitivity & specificity

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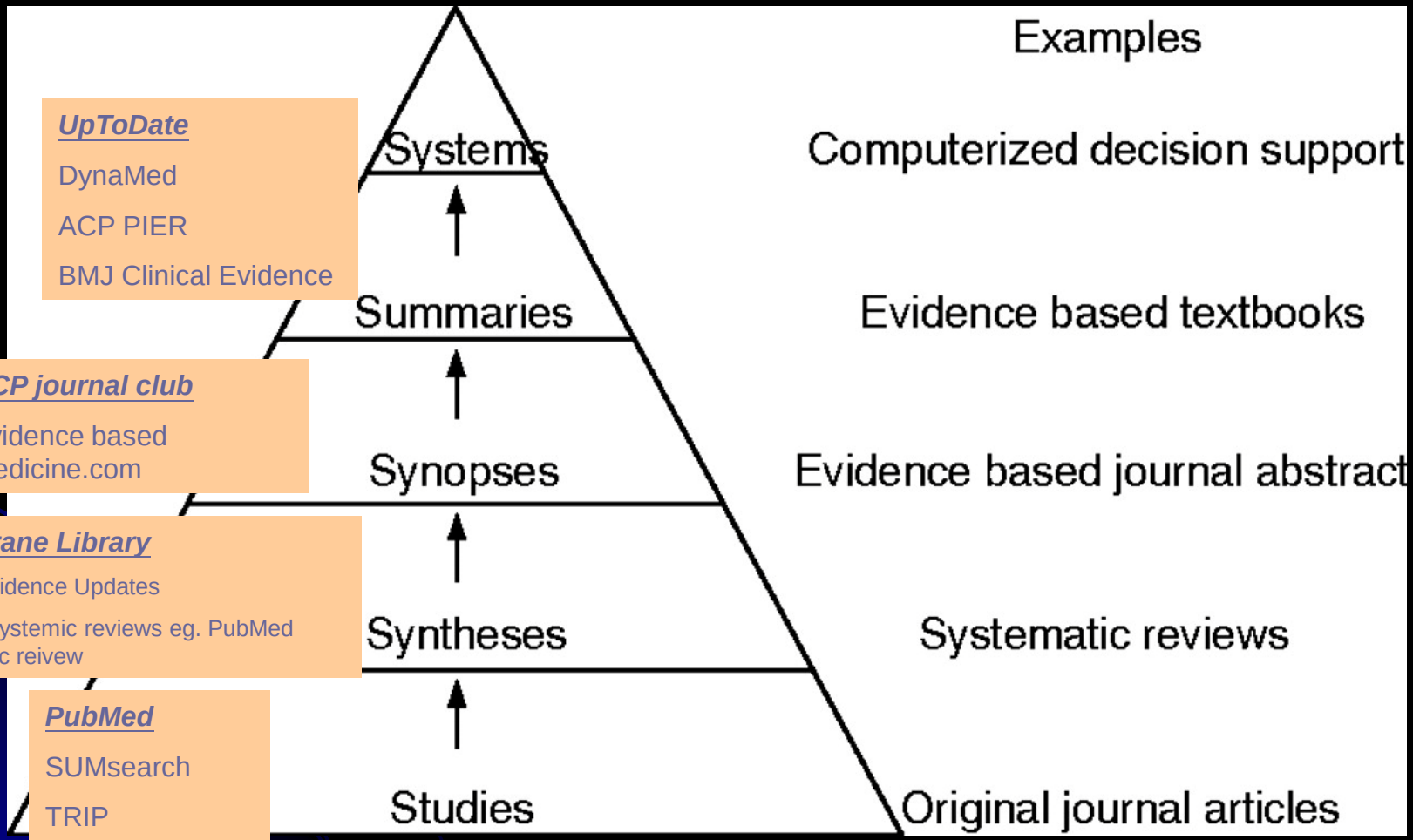

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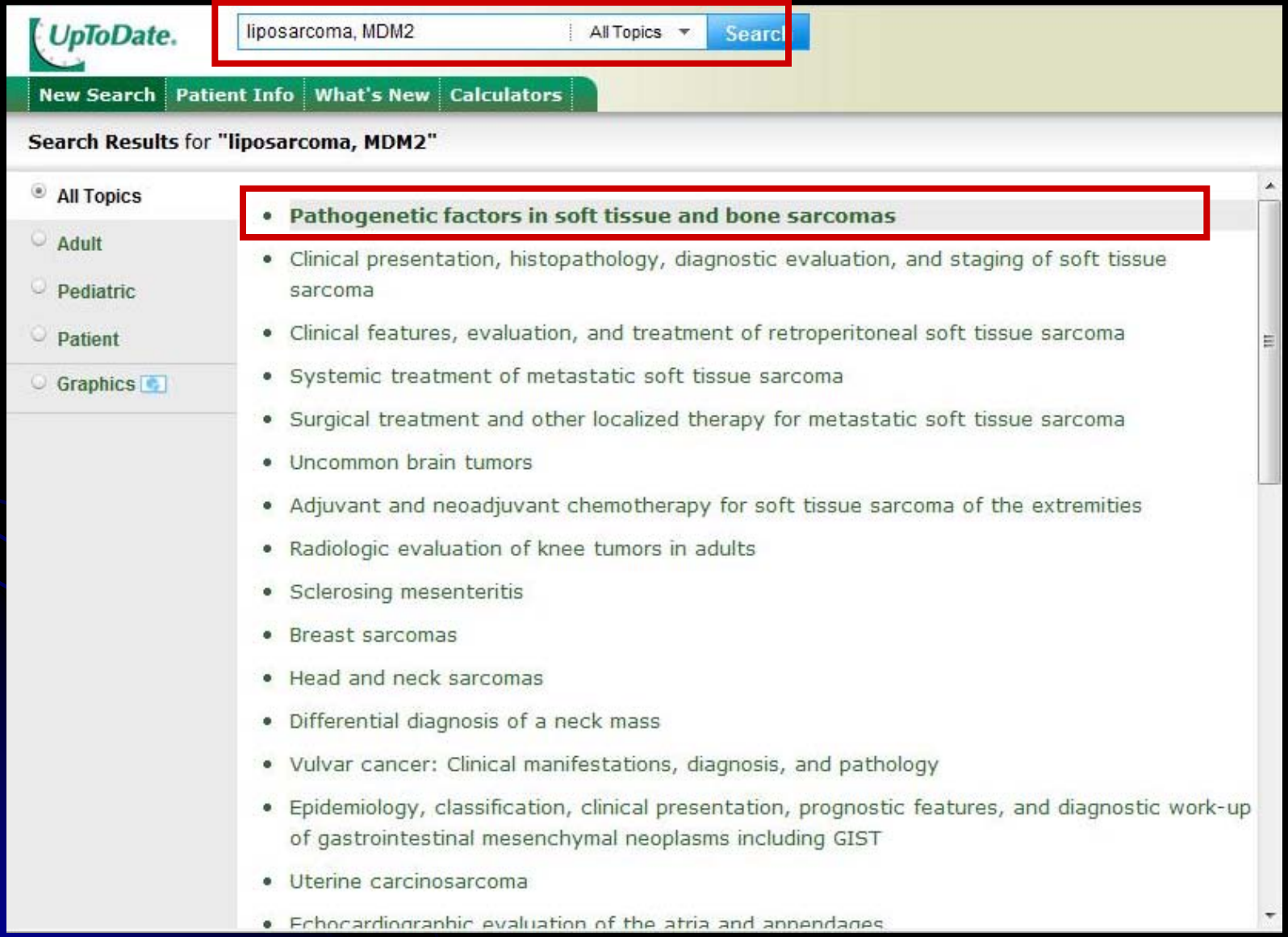
- UpToDate
  - Key words:
    - Liposarcoma, MDM2
  - Article title:
    - Pathogenetic factors in soft tissue and bone sarcomas

Summary-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Pathogenetic factors in soft tissue and bone sarcomas

TOPIC OUTLINE

Pathogenetic factors in soft tissue and bone sarcomas

Authors
Thomas F DeLaney, MD
David G Kirsch, MD, PhD

Section Editor
Robert Maki, MD, PhD

Deputy Editor
Diane MF Savarese, MD

Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: 一月 2012. | **This topic last updated:** 九月 17, 2010.

INTRODUCTION — Sarcomas are malignant tumors arising from skeletal and extraskeletal connective tissues including the system. Approximately 76 percent arise in soft tissue and the remainder in bone.

There is no clearly defined etiology in most cases of soft tissue sarcoma, but a number of associated or predisposing facto identified [1]. These include a genetic predisposition, gene mutations, radiation therapy (RT), chemotherapy, chemical carc irritation, and lymphedema. In addition, human immunodeficiency virus and human herpesvirus 8 have been implicated in the Kaposi's sarcoma. (See "AIDS-related Kaposi's sarcoma: Epidemiology and pathogenesis".)

GENETIC PREDISPOSITION — Some patients, particularly children, have a familial predisposition to cancer [1-4].

Summary

MDM2 gene — The MDM2 (murine double minute 2 homolog) gene, located at 12q15, is overexpressed in a variety of human tumors including soft tissue sarcomas [53-56]. Its gene product localizes predominantly to the nucleus, where it acts as an inhibitor of the p53 tumor suppressor gene product. The MDM2 product functions by concealing the activation domain of the p53 protein, thereby inhibiting p53 transcriptional activity [57,58].

In a series of 24 soft tissue sarcomas, an alteration in p53 was found in eight tumors and MDM2 amplification in another eight [59]. No tumor contained alterations in both genes, which is consistent with the hypothesis that p53 and MDM2 genetic alterations are alternative mechanisms for inactivating the same regulatory pathway for suppressing cell growth. In another study, 22 of 211 soft tissue sarcomas showed increased immunoreactivity to both MDM2 and p53 [60]. However, the overexpression of p53 and MDM2 proteins in the nuclei of these cells did not always correlate well with gene amplification at the MDM2 locus or mutation at the p53 gene.

CDK4 gene — The CDK4 gene, which encodes a cyclin dependent kinase, occurs in an adjacent amplicon at 12q14. Amplification of CDK4 has been found in a variety of sarcomas including liposarcomas [25,61,62]. The frequent association with MDM2 has suggested a synergistic effect in opposing p53 function [62]. A role for CDK4 amplification in the pathogenesis of soft tissue sarcomas is suggested by the fact that knockdown of CDK4 in liposarcoma cell lines or treatment of these cells with a CDK4/6 inhibitor inhibits proliferation [25].

Detection of MDM2 and CDK4 overexpression by immunohistochemical staining may be helpful in diagnosing well-differentiated and dedifferentiated liposarcomas [63].

Synopses

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  - Key words:
    - Liposarcoma, MDM2
  - Article title:
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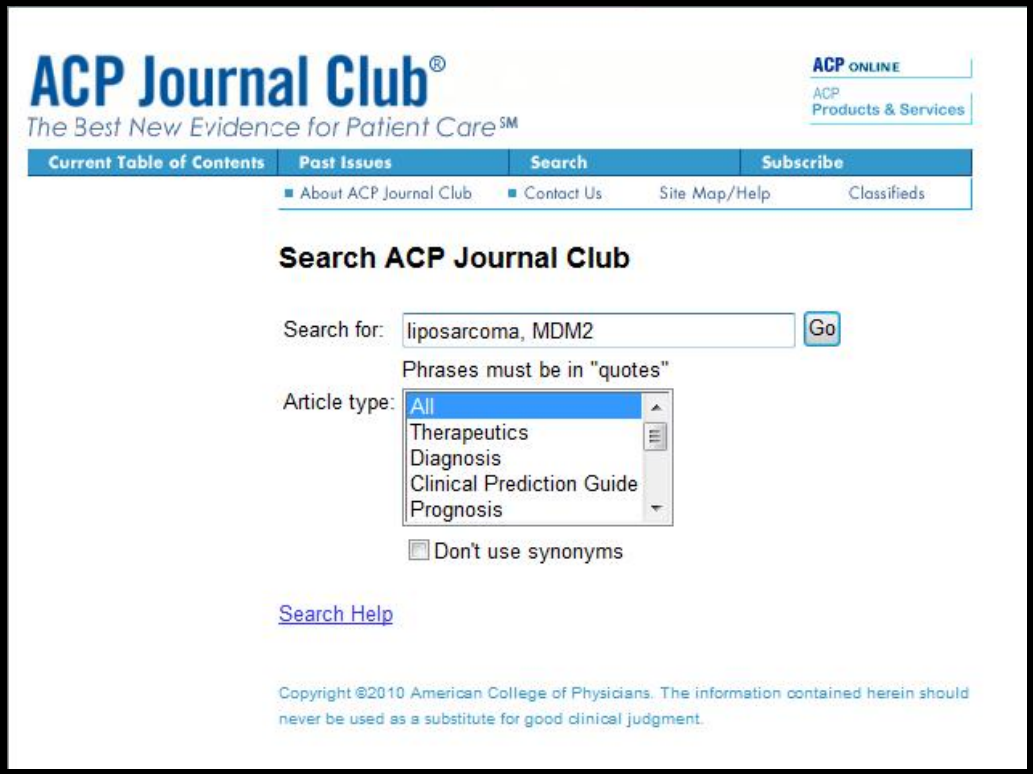

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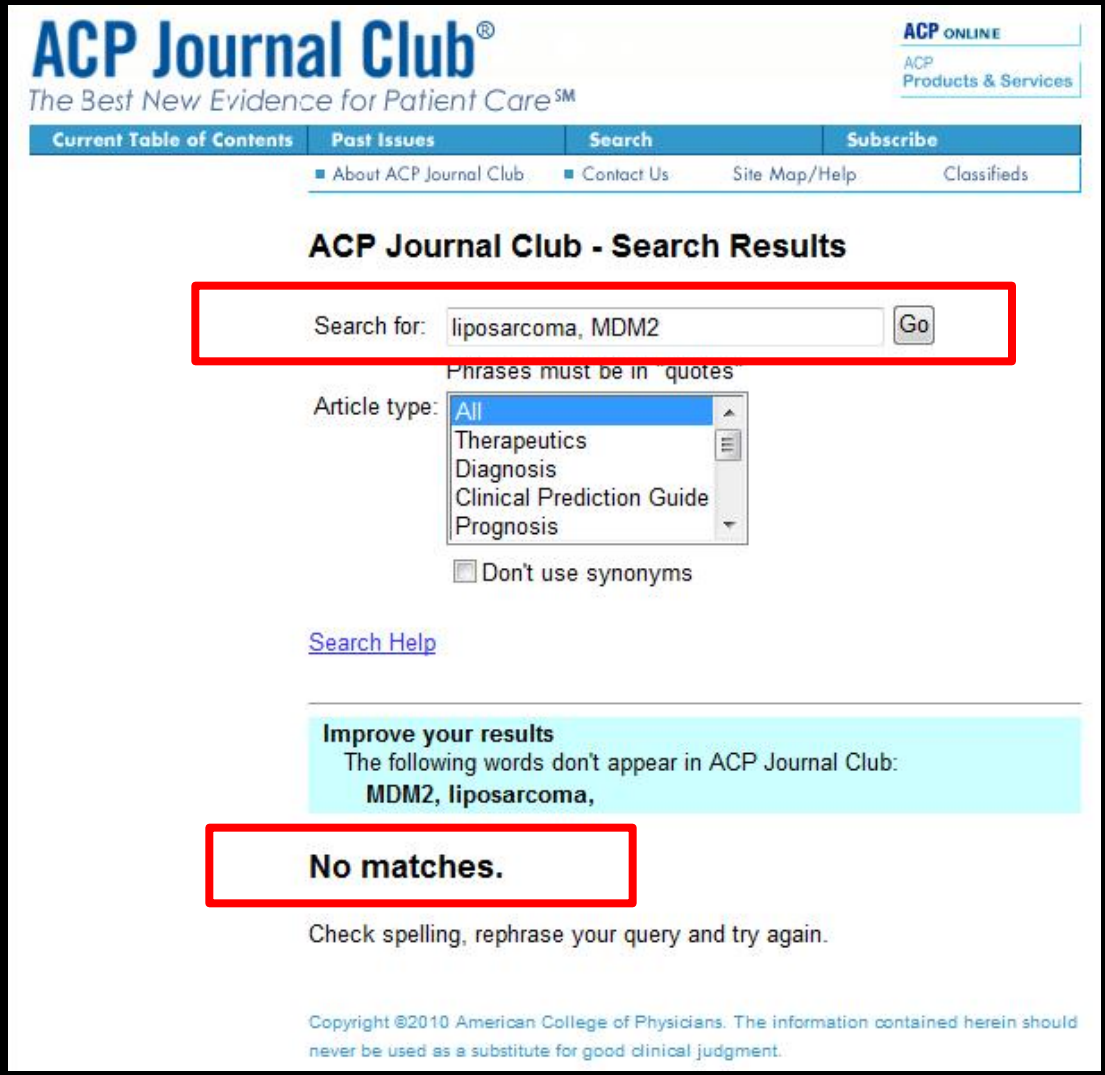

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Syntheses

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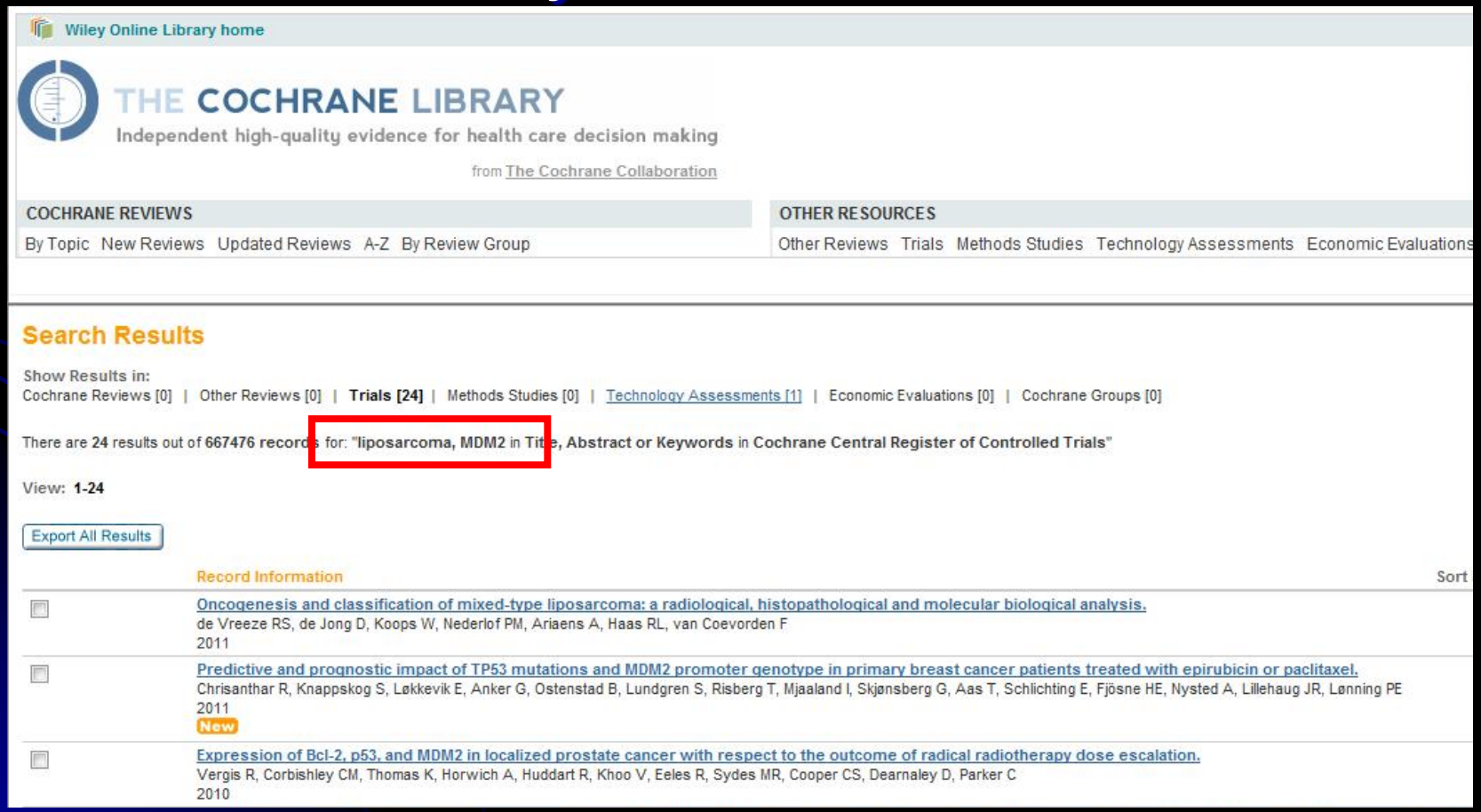
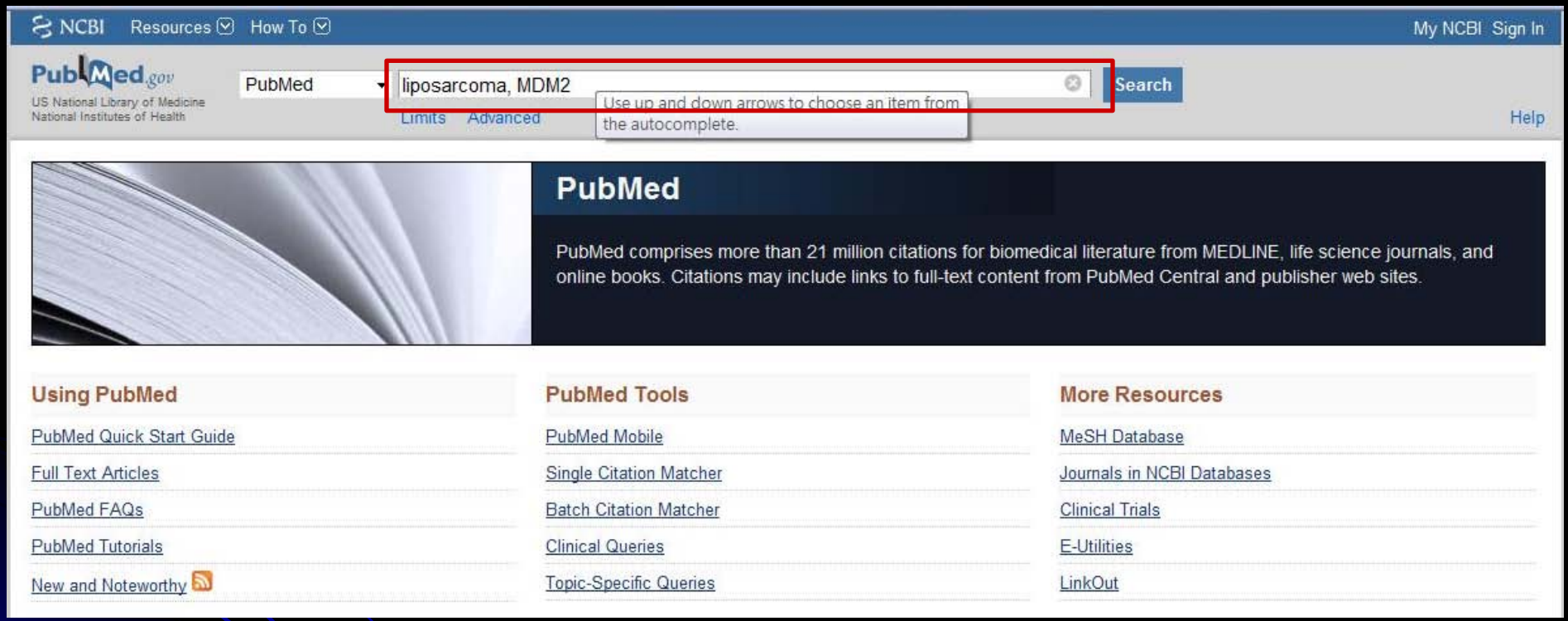


Studies

- Pubmed
  - Key words:
    - Liposarcoma, MDM2
  - Articles :
    - Diagnostic Utility of p16, CDK4, and MDM2 as an Immunohistochemical Panel in Distinguishing Well-differentiated and Dedifferentiated Liposarcomas From Other Adipocytic Tumors

Studies -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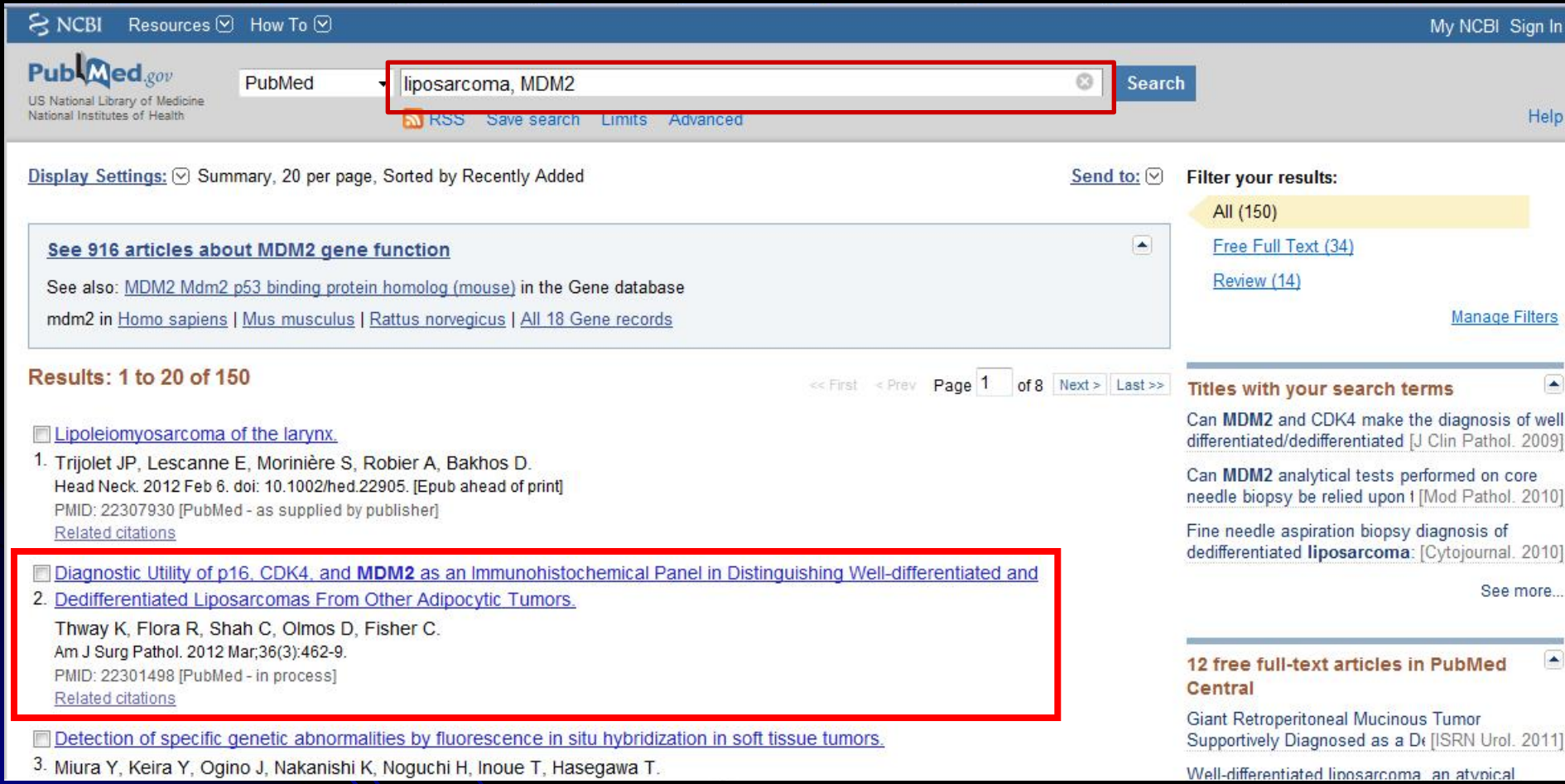
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Am J Surg Pathol. 2012 Mar;36(3):462-9.
PMID: 22301498 [PubMed - in process]
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3. Detection of specific genetic abnormalities by fluorescence in situ hybridization in soft tissue tumors.
Miura Y, Keira Y, Ogino J, Nakanishi K, Noguchi H, Inoue T, Hasegawa T.

Am J Surg Pathol. 2012 Mar;36(3):462-9.

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Thway K, Flora R, Shah C, Olmos D, Fisher C.

*Sarcoma Unit, Department of Histopathology †Sarcoma Unit, Drug Development and Medical Oncology Units, The Royal Marsden NHS Foundation Trust, London, UK.

Abstract

Adipocytic tumors are the most common type of soft tissue neoplasms. Distinguishing atypical lipomatous tumor-well-differentiated liposarcoma (WDL) from benign adipocytic neoplasms and dedifferentiated liposarcoma (DDL) from pleomorphic or myxoid liposarcoma (LPS) can be difficult. WDL and DDL characteristically harbor amplifications of the MDM2 and CDK4 cell cycle oncogenes with protein overexpression and can also overexpress the cell cycle regulator p16. We assessed the utility of immunohistochemistry for CDK4, MDM2, and p16 in the routine histopathologic diagnosis of WDL/DDL from other adipocytic tumors. Immunohistochemistry for the trio of markers was performed on 216 adipocytic neoplasms (31 WDLs, 57 DDLs, 11 myxoid LPS, 2 pleomorphic LPS, 91 lipomas (including intramuscular, fibro, angio, and ossifying subtypes), 18 spindle/pleomorphic lipomas, and 6 hibernomas. Sixty-eight percent of WDLs and 72% of DDLs expressed all 3 antigens, whereas 100% of WDLs and 93% of DDLs expressed at least 2 antigens. The sensitivity and specificity of the trio for detecting WDLs/DDLs were 71% and 98%, respectively. The sensitivity and specificity of CDK4 for detecting WDLs/DDLs were 86% and 89%, those of MDM2 were 86% and 74%, and those of p16 were 93% and 92%, respectively. The immunohistochemical trio of CDK4, MDM2, and p16 is a useful ancillary diagnostic tool that provides strong support in distinguishing WDLs and DDLs from other adipocytic neoplasms and is potentially more sensitive than previously assessed combinations of CDK4 and MDM2. p16 was the most sensitive and specific marker for detecting WDL/DDL, and the combination of CDK4 and p16 is of more discriminatory value than the combination of either with MDM2, the least sensitive and specific of the 3 markers.

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Appraisal-謹慎的文獻評讀

進行Appraisal 的文章:

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Answer	文獻試圖回答什麼問題？	是否回答我的問題？
Author	作者是誰，是否為這方面的專家	有無利益衝突
Method	RCT,cohort,case-control, case series ,	case report, expert opinion
Patient	是否隨機取樣(randomization)	取樣是否具代表性(representative)
Intervention	是否有清楚的描述(Ascertain) 是否實際可行	
Comparasion		
Outcome	是否有客觀雙盲的測量(MBO)	是否有統計學或臨床上的意義？
Time	是否清楚描述研究取樣、操作、結果測量的時間點，追蹤時間是否夠長	

AAMPICOT

- **A**: Does this paper answer your question?
  Yes.

- **A**:
  - Is the author an expert of the field?
    Yes.

Method

- Types of studies
  - Cohort study, prospective

Patients

- 取樣是否爲隨機取樣？
  - **No**
- 其特性是否接近我的病人(取樣是否具代表性)？
- - **Yes**

Intervention

- 給予實驗組的處置是否描述清楚(Ascertain)，並且是實際可行的？
  Yes

Comparison

- 給予對照組的處置是否描述清楚(Ascertain)，並且是實際可行的？

  Yes

Intervention/Comparison

- Adipocytic tumors biopsied or excised at our institution were ***prospectively*** stained for each of the 3 markers.
- All cases were formalin fixed and paraffin embedded and comprised *consecutive specimens* of adipocytic neoplasms from the routine surgical pathology workload *from 2009 to 2010*.

Intervention/Comparison

- All diagnoses were based on morphology and were agreed upon by 2 specialist soft tissue pathologists (K.T. and C.F.).
- Deparaffinized sections of each tumor were stained for CDK4, MDM2, and p16, using heat-induced epitope retrieval.
- Appropriate positive and negative controls were used throughout.

Outcome

- 是否有客觀雙盲的測量(MBO) αβ
  - No
- 是否有統計學及臨床上的意義？
  - Yes

Outcome

- Atypical lipomatous tumors (ALTs)/well-differentiated liposarcoma *(collectively referred to as WDL)* and dedifferentiated liposarcoma (DDL) form a large subgroup of LPS and are considered to represent a morphologic and behavioral spectrum of ***the same disease***.

Outcome

- ALT/WDL-DDL
  - the trio showed:
  - a sensitivity of 70.5% (95% CI, 60.9%-80.0%)
  - a specificity of 97.7% (95% CI, 95.0%-100%)
  - PPV of 95.4% (95% CI, 90.3%-100%)
  - NPV of 82.8% (95% CI, 88.2%-97.0%).
  - any 2 of 3 markers:
  - a sensitivity of 95.4% (95% CI, 88.9%-98.2%)
  - a specificity of 87.5% (95% CI, 80.7%-92.2%)
  - PPV of 84% (95% CI, 75.6%-89.9%),
  - NPV of 96.6% (95% CI, 91.5%-98.7%).

Outcome

TABLE 4. Sensitivities and Specificities of Expression of the Trio of CDK4, MDM2, and p16 and of Individual Markers in Diagnosing ALT-WDL and DDL

	WDL-DDL Group				Sensitivity (%)	
Antibody	Sensitivity	Specificity	PPV	NPV	WDL	DDL
Trio	70.5% (62/88)	97.7% (125/128)	95.4% (62/65)	82.8% (125/151)	67.7	71.9
p16	93.2% (82/88)	92.2% (118/128)	89.1% (82/92)	95.2% (118/124)	96.8	93.0
CDK4	86.4% (76/88)	89.1% (114/128)	84.8% (78/92)	91.9% (114/124)	87.1	91.2
MDM2	86.4% (76/88)	74.2% (95/128)	78.4% (76/97)	86.4% (95/110)	80.6	82.5
p16/CDK4	83.0% (73/88)	97.7% (125/128)	96.1% (73/76)	89.3% (125/140)	83.9	82.5
p16/MDM2	77.3% (68/88)	95.3% (122/128)	91.9% (68/74)	85.9% (122/142)	80.6	75.4
CDK4/MDM2	76.1% (67/88)	89.1% (114/128)	82.7% (67/81)	84.4% (114/135)	80.6	82.5
Any 2 positive	95.4% (84/88)	87.5% (112/128)	84.0% (84/100)	96.6% (112/116)	96.8	93.0

Time

- 文獻發表時間: 2012
- 是否清楚描述研究取樣、操作、結果測量的時間點：yes
- 追蹤時間是否夠長？Probably yes

證據等級

Level	與[治療/預防/病因/危害]有關的文獻
1a	用多篇RCT所做成的綜合性分析(SR of RCTs)
1b	單篇RCT(有較窄的信賴區間)
1c	All or none
2a	用多篇世代研究所做成的綜合性分析
2b	**單篇cohort及低品質的RCT**
2c	Outcome research / ecological studies
3a	SR of case-control studies
3b	Individual case-control studies
4	Case-series(poor quality :cohort / case-control studies)
5	沒有經過完整評讀醫學文獻的專家意見

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

Critical Appraisal of Diagnostic Accuracy Study
“診斷工具”的評析

- Are the results of the study valid (效度如何)？

Was the diagnostic test evaluated in a representative spectrum of patients

是否經過具有代表性的病人群測試過？

■是　　□否　　□不清楚

評論：1.每一個adipocytic tumors皆使用三種marker去染色
2.是consecutive specimens(連續選擇)→減少偏差
3.研究方法所述之研究檢體具有代表性

Was the reference standard ascertained regardless of the index test result

標準診斷工具做確診時不知道指標診斷工具的結果？

■是　　□否　　□不清楚

評論：所有病人檢體皆有接受標準診斷工具(reference standard)-CDK4與MDM2-之免疫化學染色

Was there an independent, blind comparison between the index test and an appropriate gold standard of diagnosis

標準診斷工具與指標診斷工具是在獨立且雙盲的情況下進行比較？

□是　　■否　　□不清楚

評論：1.標準診斷工具(CDK4和MDM2)之選擇有基因層面的根據，故可以說是恰當的。

2.CDK4,MDM2,p16之免疫化學染色判讀並非獨立執行，此研究亦沒有雙盲。檢查結果之判讀者可能知道另一項檢查之結果(文獻中並無詳述)

- Each tumor was assessed according to a 4-tier system: absent, weak, moderate, or strong for intensity of antibody reaction. Immunoreactivity was semiquantitatively evaluated as negative (0% of cells stained), focally positive (1% to 10% of cells stained), multifocally positive (11% to 50% of cells stained), or diffusely positive (>50% of cells stained). Immunoreactivity was evaluated by 4 pathologists: 2 soft tissue surgical pathology fellows (R.F. and C.S.) and 2 specialist soft tissue pathologists (K.T. and C.F.), after which a consensus score was reached.

Critical Appraisal of Diagnostic Accuracy Study
“診斷工具”的評析

- What were the results (結果是甚麼)？

Are test characteristics presented
呈現指標診斷工具的特性？

TABLE 4. Sensitivities and Specificities of Expression of the Trio of CDK4, MDM2, and p16 and of Individual Markers in Diagnosing ALT-WDL and DDL

	WDL-DDL Group				Sensitivity (%)	
Antibody	Sensitivity	Specificity	PPV	NPV	WDL	DDL
Trio	70.5% (62/88)	97.7% (125/128)	95.4% (62/65)	82.8% (125/151)	67.7	71.9
p16	93.2% (82/88)	92.2% (118/128)	89.1% (82/92)	95.2% (118/124)	96.8	93.0
CDK4	86.4% (76/88)	89.1% (114/128)	84.8% (78/92)	91.9% (114/124)	87.1	91.2
MDM2	86.4% (76/88)	74.2% (95/128)	78.4% (76/97)	86.4% (95/110)	80.6	82.5
p16/CDK4	83.0% (73/88)	97.7% (125/128)	96.1% (73/76)	89.3% (125/140)	83.9	82.5
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Apply-臨床應用

結合醫學倫理方法

將study的結果應用在病人身上

醫療現況

目前p16之免疫化學染色並未常規使用於區分well-differentiated LPS與lipoma。p16在LPS之角色目前所知甚少、仍需進一步研究。

病人意願

病人對於選用何種IHC(Immunohistochemistry免疫組織化學染色)做診斷沒有表示意願。

生活品質

脂肪腫瘤良惡性之診斷對於日後的預後追蹤有輔助價值。在本案例中因病人已使用MDM2輔助診斷出well-differentiated LPS，故是否選用p16做輔助診斷對病人之生活品質並無影響。

社會脈絡

並無病人家庭或家族方面之因素影響IHC之使用。但因為p16在LPS之角色仍須進一步研究，目前在病理實驗室p16仍屬做study時才使用的IHC，並非常規使用。如要使用還須特別要求。

總結與討論：

- 使用p16之IHC確實在已確定爲脂肪細胞腫瘤的情形下，在區分well-differentiated liposarcoma與其它相似之良性脂肪細胞腫瘤有著很高的sensitivity與specificity
- 雖然沒有應用在本個案上，但在進一步研究出來後，可以考慮日後在患有脂肪細胞腫瘤之病人做爲常規使用(但在目前需要特別要求醫檢師幫忙染色)。因爲腫瘤之良惡性診斷對臨床醫師在病人之追蹤預後上有很大影響。

Audit-自我評估

在「提出臨床問題」方面的自我評估

- 我提出的問題是否具有臨床重要性？有
- 我是否明確的陳述了我的問題？
  - 我的foreground question 是否可以清楚的寫成PICOT？可
  - 我的background question是否包括what, when, how, who等字根？有
- 我是否清楚的知道自己問題的定位？（亦即可以定位自己的問題是屬於診斷上的、治療上的、預後上的或流行病學上的），並據以提出問題？知道，是屬於診斷上的
- 對於無法立刻回答的問題，我是否有任何方式將問題紀錄起來以備將來有空時再找答案？有

在「搜尋最佳證據」方面的自我評估

- 我是否已盡全力搜尋？是
- 我是否知道我的問題的最佳證據來源？是
- 我是否從大量的資料庫來搜尋答案？是
- 我工作環境的軟硬體設備是否能支援我在遇到問題時進行立即的搜尋？是
- 我是否在搜尋上愈來愈熟練了？是
- 我會使用「斷字」、布林邏輯、同義詞、MeSH term，限制（limiters)等方法來搜尋？我對其中一些搜尋方式還不熟悉
- 我的搜尋比起圖書館人員或其他對於提供病人最新最好醫療有熱情的同事如何？他們有很多值得我學習的地方

關於「嚴格評讀文獻」方面的自我評估

- 我是否盡全力做評讀了？是
- 我是否了解sensitivity, specificity的意義？了解
- 我是否了解Positive predictive value (PPV), Negative predictive value (NPV)的意義？了解
- 我是否了解worksheet每一項的意義？是，但統計學方面的知識需要再加強
- 評讀後，我是否做出了結論？是

關於「應用到病人身上」的自我評估

- 我是否將搜尋到的最佳證據應用到我的臨床工作中？是，但這個個案沒有
- 我是否能將搜尋到的結論如sensitivity, specificity用病人聽得懂的方式解釋給病人聽？可以
- 當搜尋到的最佳證據與實際臨床作為不同時，我如何解釋？會參考文獻證據但仍以實際臨床為主

改變「醫療行為」的自我評估

- 當最佳證據顯示目前臨床策略需改變時，我是否遭遇任何阻止改變的阻力？

  目前為止還沒有經驗

- 我是否因此搜尋結果而改變了原來的診斷策略？做了那些改變？

  在此個案上診斷策略並無改變。但在日後，在確定為脂肪細胞腫瘤的前提下，對於區分well-differentiated liposrcoma和lipoma，我也會考慮選擇染p16之IHC做為診斷之輔助工具

效率評估

- 這篇報告，我總共花了多少時間？共約30個小時。
- 我是否覺得這個進行實證醫學的過程是值得的？是。藉由EBM技巧，搜尋關於疾病診斷工具的文獻，得到的結果對實際診斷疾病有相當的輔助作用，我覺得很值得。
- 我還有那些問題或建議？目前暫時沒有。

Thank you for your attention!!