TAIPEI VETERANS GENERAL HOSPITAL PRACTICES GUIDELINES FOR

Cancer of unknown primary origin

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壹、前言

Cancer of unknown primary (CUP) is defined as a tissue-proven malignancy which the primary tumor cannot be identified even after thorough examination. The prevalence rate of CUP among all types of cancer is around 3% in the world and ranked the 7th cancer occurrence (1). In Taiwan, because of the health care system, most CUP patients will eventually be referred to medical centers and took care by medical oncologists. Incidence of CUP in Sweden has decreased since late 90s but the survival has not been improved since then (2). From the cancer register system of Taipei Veterans General Hospital (VGHTPE), the patients' number seemed not to decrease even the imaging tools are improved for the primary tumor detection during last decade (3). Meanwhile, most CUP patients are diagnosed at elder age more than 65 y/o. From the 10-year cohort of VGHTPE, the age between 70-79 y/o ranked the highest occurrence rate of CUPs and the second highest group is between 80-89 y/o (4).

The major involved organs account for the largest tumor burden and related symptoms/signs of CUP patients. In the recent review, the most commonly involved metastatic sites are liver (40–50%) following by lymph nodes (35%), lungs (31%), bones (28%), and the brain (15%) (1). The top ranked four sites are the same as our VGHTPE cohort (bone 26.3%, lymph nodes 24%, liver 21.2%, lung 12.8%), although the sequence is a little different (3). The common pathologic subtypes are classified as unclassifiable carcinoma (46.4%) followed by adenocarcinoma (39.7%). (3). The approach for the CUP includes general survey for the possibility of tumor origin. The current popular categorization is to separate CUPs into the two main groups, which are called "favorable" and "unfavorable". For the favorable group patients, the treatment will be given according to the most likely cancer types. Criteria for the favorable group CUPs is listed as: 1) Axillary lymph node metastatic adenocarcinoma in woman; 2) Mesentery metastatic adenocarcinoma in woman; 3) Male osteoblastic bone metastasis combining with elevated serum PSA; 4) Single inguinal lymph node metastasis of squamous cell carcinoma; 5) Undifferentiated midline germ cell like tumor. For accurately categorizing patients, comprehensive survey at initial diagnosis is very important. In general, thorough history taking and physical examination, appropriate imaging and serum biomarkers analysis, as well as good pathologic reading of tumor tissues are all necessary.

Most CUP patients belong to unfavorable subsets and the most common subset is visceral metastatic disease (1). In a systematic review of more than 700 unfavorable CUP patients, the treatment response was less than 20% and median survival was only around 6–7 months (1). Several clinical factors have been associated with the prognosis of unfavorable CUPs including leukocytosis, serum LDH and albumin level (3, 5). The modified inflammation-based Glasgow Prognostic Score (mGPS) was also used to evaluate the CUP prognosis and compared with neutrophil/lymphocyte ratio, which both showed a good prediction (6). Until now, there is still no standard treatment for unfavorable CUPs. Several phase II trials have suggested platinums, taxanes, 5-FU and gemcitabine, etc. may be benefit for these patients. A phase II trial also showed efficacy in treated/untreated CUP patients, especially with high PDL1 expression (7-9, 11-18, 22).

In the era of personalized medicine, several genome-guided treatments by approaching the target drugs for specific mutations has been applied for the CUPs therapy. The techniques include microarray-based gene panel for tumor tissue, assay with a gene panel for real-time quantitative RT-PCR from tumor genome or microRNA, and gene sequencing from liquid biopsy samples. However, few assay has been approved by US Food and Drug Administration. Several specific oncogenes, such as MYC, RAS, TP53, VEGFA, or MMP have been shown with up-regulation in CUPs (1). The circulating tumor cells in the peripheral blood have been detected with certain ratio (62.5%) in CUP patients and were recorded in a small study (10). To sum up, the molecular signature for CUP has not been well-established and further researches are warranted.

Uncertainties treatment, diagnosis, and poor prognosis of CUPs will result in significant psychosocial stress. One study showed that anxiety as well as depression more commonly happened in CUPs than other cancer types. (20) So early psychosocial support and palliative care interventions from hospice caring system should also be recommended as regular practice.

In conclusion, CUPs is still a difficult type of cancer for diagnosis and treatment. The prognosis is especially poor in unfavorable CUPs. Multidiscipline approach, as well as searching for the new clinical trials for diagnosis, therapy and surveillance is necessary for these patients.

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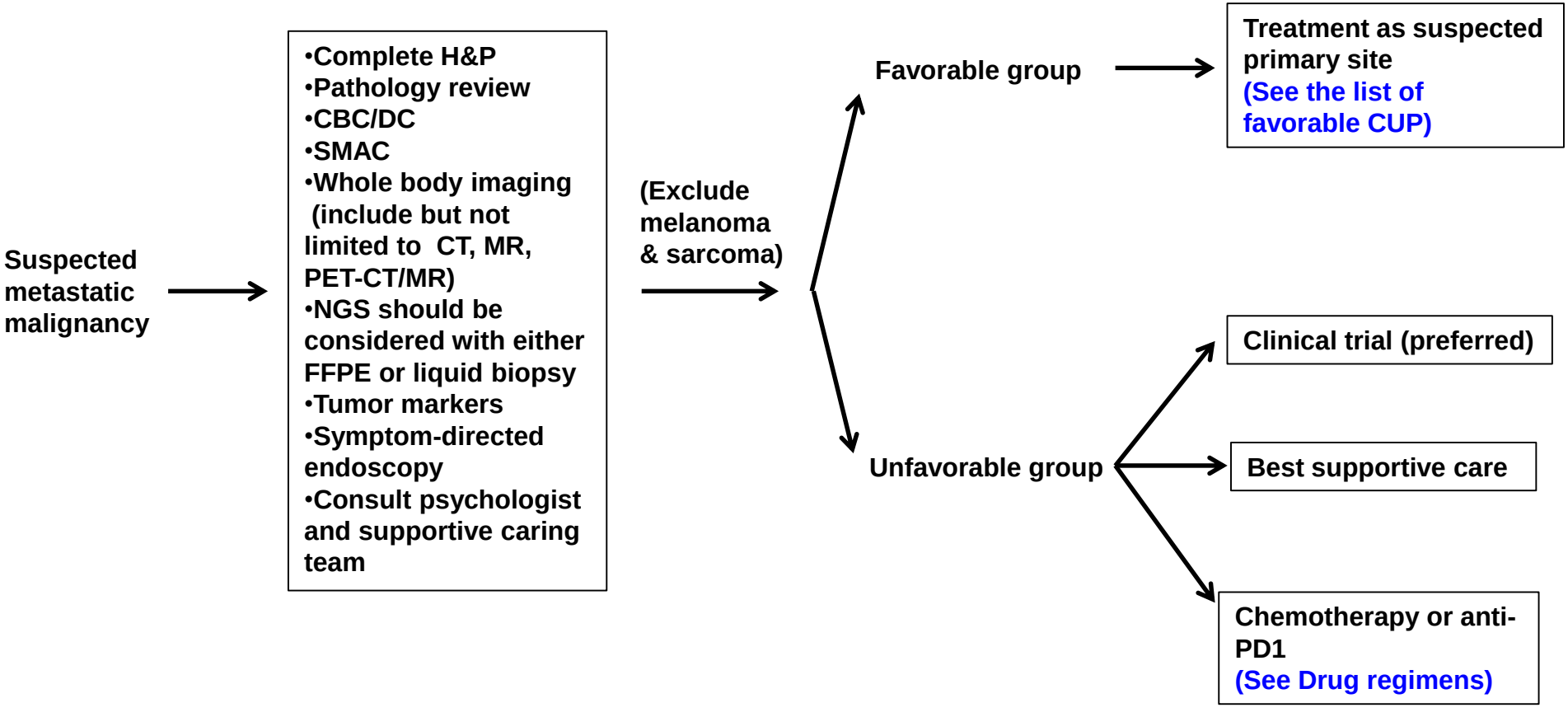
貳、重要臨床準則

Treatment guidelines



List of favorable group CUP

• Women with lone axillary lymph nodes containing adenocarcinoma	→	*Treated as breast cancer*
• Poorly differentiated or undifferentiated carcinoma with characteristics of extragonadal germ cell tumor syndrome	→	*Treated as germ cell tumor*
• Women with diffuse peritoneal carcinomatosis (papillary adenocarcinoma)	→	*Treated as ovarian cancer*
• Squamous cell carcinoma involving upper cervical lymph nodes	→	*Treated as head and neck cancer (squamous cell carcinoma)*
• Squamous cell carcinoma involving solitary inguinal lymph node	→	*Treated as skin cancer (squamous cell carcinoma)*
• Man with osteoblastic bone metastasis and elevated serum PSA level	→	*Treated as prostate cancer*

Drug regimens*

- Carboplatin/Paclitaxel q3wk (7)
- Carboplatin/Paclitaxel/Etoposide q3wk (11)
- Carboplatin/Docetaxel q3wk (8)
- Cisplatin/Gemcitabine q3wk (12)
- Gemcitabine/Docetaxel q3wk (9)
- Cisplatin/Docetaxel q3wk (8, 13)
- Irinotecan/Carboplatin q4wk (14)
- Irinotecan/Gemcitabine q3wk (15)
- Cisplatin/5-FU (16)
- Cisplatin/Paclitaxel q3wk (17)
- Oxaliplatin/capecitabine q3wk § (18)
- Nivolumab (22)

**Other empiric chemotherapy should be given according to physicians' judgement*
§After at least 1 previous treatment

Immunohistochemistry markers for CUP*

Markers	Cell type
CK7/CK20	Carcinoma
CK5/CK6, p63/p40	Squamous cell carcinoma
S100, SOX10	Melanoma
LCA ± CD20	Lymphoma
OCT3/4 ± SALL4	Germ cell tumor
WT1, Calretinin, Mesothelin	Mesothelial tumor

**IHC markers is suggested according to pathologists case by case*

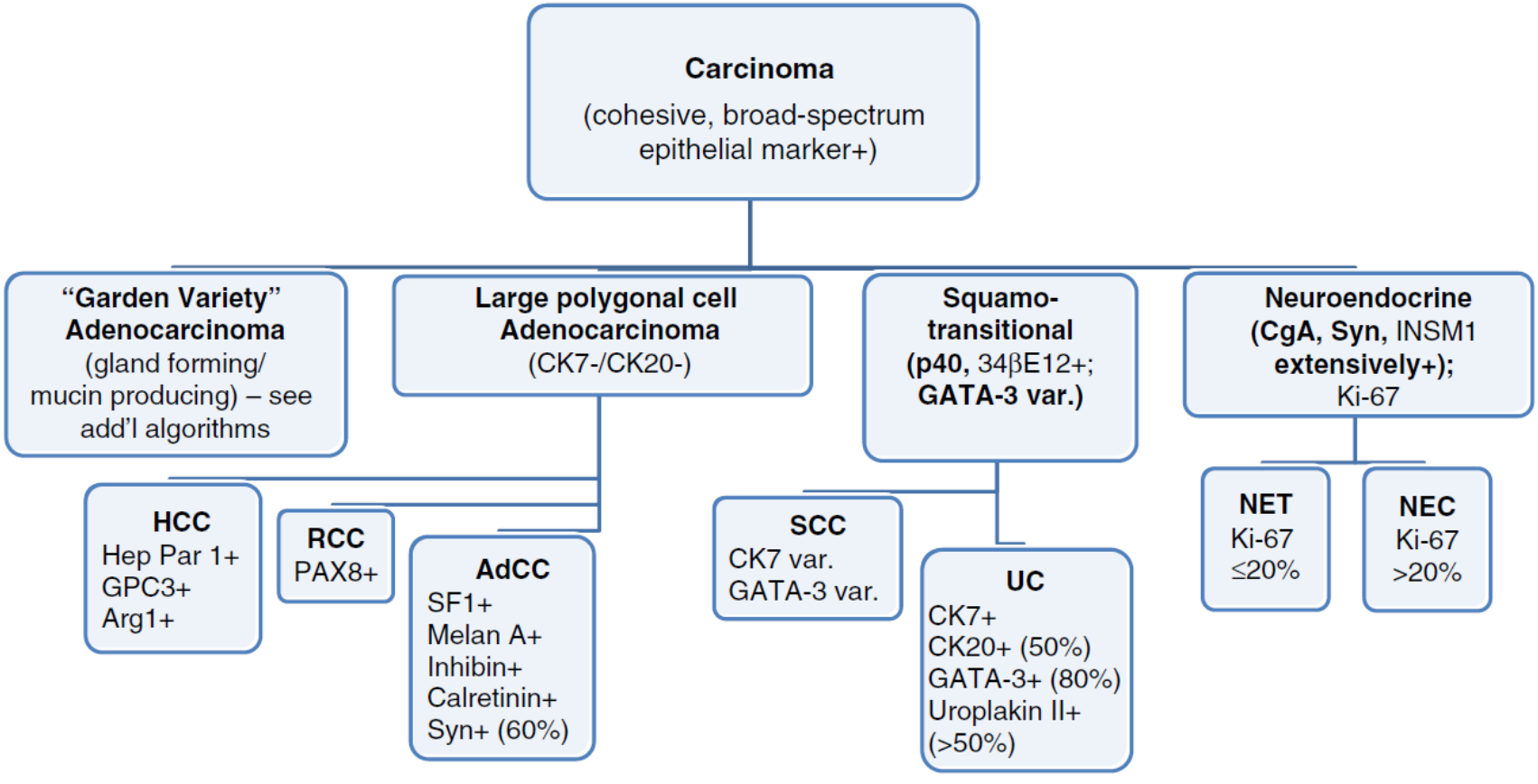


FIGURE 1. Algorithmic approach to diagnosis of four carcinoma types. AdCC indicates adrenal cortical carcinoma; Arg1, arginase-1; CgA, chromogranin A; GPC3, glypican-3; HCC, hepatocellular carcinoma; NEC, poorly differentiated neuroendocrine carcinoma; NET, well-differentiated neuroendocrine tumor; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; Syn, synaptophysin; UC, urothelial carcinoma. Please see this image in color online.

Adv Anat Pathol 2020;27:114–163

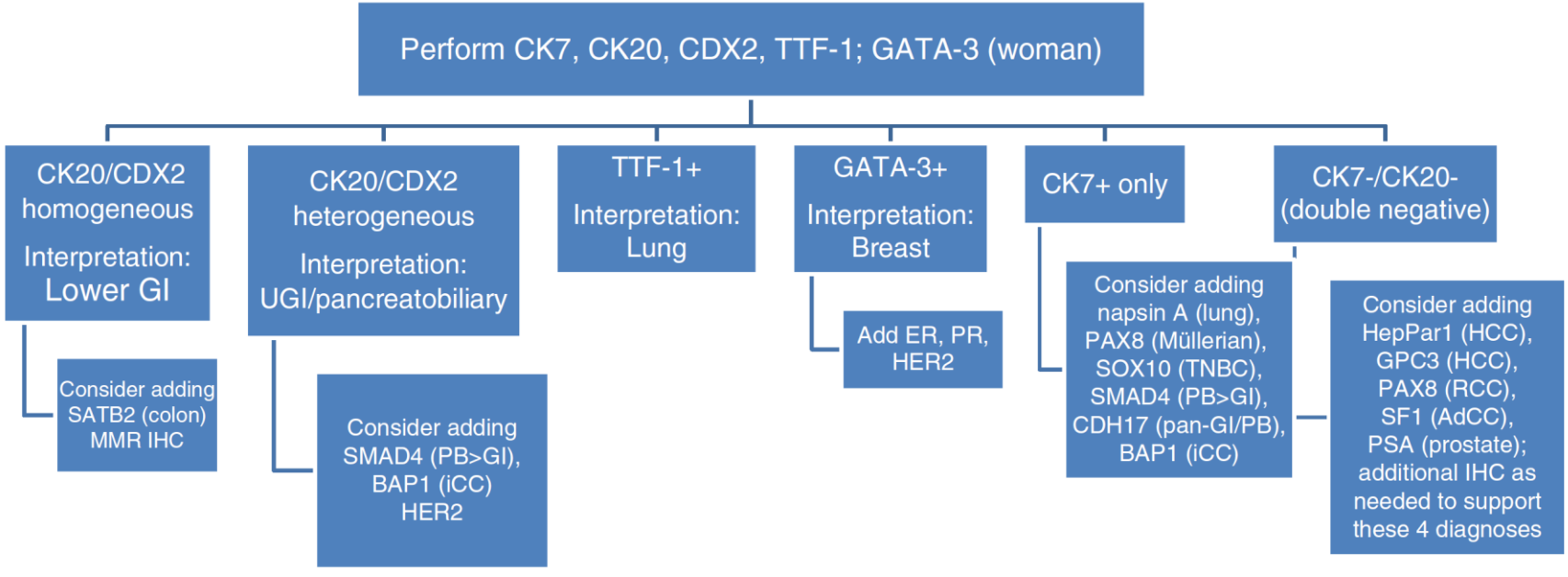


FIGURE 2. Immunohistochemical algorithm for "garden variety" adenocarcinoma in the liver. AdCC indicates adrenal cortical carcinoma; ER, estrogen receptor; GI, gastrointestinal; GPC3, glypican-3; HCC, hepatocellular carcinoma; iCC, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; PB, pancreatobiliary; PR, progesterone receptor; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; UGI, upper gastrointestinal. Please see this image in color online.

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The modified Glasgow Prognostic (mGPS) score

Criteria	Points allocated
CRP ≤ 10mg/l and albumin ≥ 3.5 g/dl	0
CRP > 10mg/l	1
CRP > 10mg/l and albumin <3.5 g/dl	2

Neutrophil/Lymphocyte ration (NLR)

NLR < 5	Good
NLR > 5	Poor

**Both mGPS score (19) or NLR (6) could be used as the independently prognostic factors*

EORTC QLQ-C30 台灣中文版*

我們很希望瞭解有關您和您的健康狀況。請您親自回答以下所有的問題，圈選最合適於您的答案。答案中沒有「對」或「錯」。您所提供的資料將完全保密。

受訪者代碼：_____（由研究者依照順序編列或用姓名譯音英文縮寫）
您的生日：____年____月____日
今天的日期：____年____月____日

	完全沒有	有一點	相當多	非常多
1. 您從事一些費力的活動，如攜帶重的購物袋或手提箱，是否有困難？	1	2	3	4
2. 您從事長距離步行，是否有困難？	1	2	3	4
3. 您在戶外從事短距離步行，是否有困難？	1	2	3	4
4. 您在白天是否需要待在床上或椅子上？	1	2	3	4
5. 您進食、穿衣、洗澡或上廁所需要別人幫助嗎？	1	2	3	4
在過去一星期內（過去七天內）：	**完全沒有**	**有一點**	**相當多**	**非常多**
6. 您在從事工作或日常活動上是否受到限制？	1	2	3	4
7. 您在從事嗜好或休閒活動上是否受到限制？	1	2	3	4
8. 您呼吸會喘嗎？	1	2	3	4
9. 您曾感到疼痛嗎？	1	2	3	4
10. 您需要休息嗎？	1	2	3	4
11. 您睡眠曾有困難嗎？	1	2	3	4
12. 您曾感到虛弱嗎？	1	2	3	4
13. 您曾缺乏食慾嗎？	1	2	3	4
14. 您曾感到噁心嗎？	1	2	3	4
15. 您曾嘔吐嗎？	1	2	3	4

在過去一星期內（過去七天內）：	**完全沒有**	**有一點**	**相當多**	**非常多**
17. 您曾腹瀉嗎？	1	2	3	4
18. 您疲倦嗎？	1	2	3	4
19. 疼痛干擾您的日常活動嗎？	1	2	3	4
20. 您曾否難將注意力集中在一些事情上，如看報紙或看電視？	1	2	3	4
21. 您覺得緊張嗎？	1	2	3	4
22. 您感到憂慮嗎？	1	2	3	4
23. 您覺得容易發怒嗎？	1	2	3	4
24. 您覺得情緒低落嗎？	1	2	3	4
25. 您曾感到記憶困難嗎？	1	2	3	4
26. 您的身體狀況或醫療過程是否曾干擾您的家庭生活？	1	2	3	4
27. 您的身體狀況或醫療過程是否曾干擾您的社交活動？	1	2	3	4
28. 您的身體狀況或醫療過程是否曾造成您財務上的困難？	1	2	3	4

以下問題，請在 1 到 7 之間圈選最適合您的答案。

29. 您如何評定過去一星期內（過去七天內）您整體的健康？

1　2　3　4　5　6　7
非常差　極好

30. 您如何評定過去一星期內（過去七天內）您整體的生活品質？

1　2　3　4　5　6　7
非常差　極好

*Suggested for patient life quality survey

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