WCJD 世界华人消化杂志®

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世界华人消化杂志 2017年8月8日; 25(22): 2045-2050

DOI: 10.11569/wcjd.v25.i22.2045

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

KRAS/BRAF基因与结肠癌糖代谢研究现状

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收稿日期: 2017-03-31
修回日期: 2017-06-19
接受日期: 2017-06-27
在线出版日期: 2017-08-08

Association between *KRAS/BRAF* gene and glucose metabolism in colon cancer

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Received: 2017-03-31
Revised: 2017-06-19
Accepted: 2017-06-27

Published online: 2017-08-08

Abstract

Positron emission tomography (PET)/computed tomography (CT), a diagnostic tool to evaluate glucose metabolic activity by measuring accumulation of FDG (^{18}F-fluorodeoxy glucose, an analogue of glucose), can be used for detecting tumors, monitoring treatment response and predicting patients' prognosis in colon cancer. *KRAS/BRAF* gene test has been used to determine the choice of target therapy for colon cancer and to predict its prognosis. It has been reported that FDG-PET/CT has a potential in predicting mutational status and therefore may play an important role in determining therapeutic strategies by non-invasively predicting treatment response to anti-epidermal growth factor receptor (EGFR) therapy. However, it is inconclusive whether *KRAS/BRAF* gene mutation correlates with glucose metabolism detected by PET/CT in colon cancer. In this review, we summarize the current findings discussing the underlying mechanisms between glucose metabolism and *KRAS/BRAF* gene mutation in colon cancer.

Key Words: Colon cancer; *KRAS/BRAF* gene; PET/CT; GLUT-1

Liu L, Huang JB, Qiu DS. Association between *KRAS/BRAF* gene and glucose metabolism in colon cancer. Shijie Huaren Xiaohua Zazhi 2017; 25(22): 2045-2050 URL: http://www.wjgnet.com/1009-3079/full/v25/i22/2045.htm DOI: http://dx.doi.org/10.11569/wcjd.v25.i22.2045

背景资料
结肠癌是我国消化系统常见的恶性肿瘤之一, 发病率年均上升3%-4%. 结肠癌发病与基因突变关系密切, *KRAS/BRAF*基因检测对结肠癌靶向治疗及判断预后具有重要意义, 有文献报道^{18}F-FDG-PET/CT作为一种无创的检查方式, 能预测结肠癌*KRAS/BRAF*突变状态, 从而为临床提供重要参考.

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研发前沿

^{18}F-FDG-PET/CT显像作为一种无创的检查手段, 对预测结直肠癌*KRAS/BRAF*基因状态具有重要价值. 然而FDG-PET/CT显像预测结直肠癌*KRAS/BRAF*突变准确性在60%左右, 且与研究对象、实验方法有密切相关, 是否存在其他基因影响RAS-RAF-MAPK通路传导尚未可知, 现有研究对FDG-PET/CT显像预测结直肠癌*KRAS/BRAF*突变尚有争议, 尚需大样本研究及探索FDG-PET参数来提高FDG-PET/CT显像预测结直肠癌*KRAS/BRAF*突变的准确性, 从而为结肠癌(colorectal cancer, CRC)的靶向治疗及预后提供重要参考.

摘要

正电子发射断层成像术(positron emission tomography, PET)/计算机断层扫描(computed tomography, CT)显像可用于结肠癌的诊断、监测疗效和预后评估. ^{18}F标记葡萄糖(2-fluorine-18-fluoro-2-deeoxy-D-glucose, ^{18}F-FDG)是PET/CT常用显像剂, 可以反映结肠癌活体组织葡萄糖代谢. *KRAS/BRAF*基因检测常用于结肠癌靶向治疗方案的选择及评估其治疗效果. 文献报道^{18}F-FDG-PET/CT显像可预测结肠癌*KRAS/BRAF*基因状态, 能以无创的方式预测结肠癌抗表皮生长因子受体靶向治疗效果. 目前国内有关*KRAS/BRAF*基因与结肠癌糖代谢的研究相对较少, 本文结合近期的相关文献进行概述.

关键词: 结肠癌; *KRAS/BRAF*基因; 正电子发射断层扫描; 葡萄糖转运体-1

核心提要: *KRAS/BRAF*基因检测对结肠癌的治疗及判断预后具有重要意义, 肿瘤细胞微环境(低糖或低氧)与*KRAS/BRAF*突变以及FDG摄取存在明显相关性, ^{18}F-FDG-PET/CT显像作为一种无创的检查手段, 对预测结直肠癌*KRAS/BRAF*基因状态具有重要意义, 从而为临床提供重要参考.

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0 引言

结肠癌是我国消化系统常见的恶性肿瘤之一, 发病率年均上升3%-4%. 目前, 我国结直肠癌发病率虽然低于欧美发达国家, 但我国结直肠癌发病和死亡例数均居第1位, 分别占世界发病和死亡总例数的18.6%和20.1%[1]. 结肠癌发病与基因突变关系密切, 研究[2,3]表明左半结肠癌与抑癌基因(例如*APC*、*P53*)的失活和*KRAS*基因突变等相关, 而右半结肠癌与癌基因激活、*BRAF*基因突变、CpG岛甲基化表型等相关. *KRAS/BRAF*基因检测对结肠癌靶向治疗及判断预后具有重要意义, ^{18}F标记葡萄糖(2-fluorine-18-fluoro-2-deeoxy-D-glucose, ^{18}F-FDG)-正电子发射断层成像术(positron emission tomography, PET)/计算机断层扫描(computed tomography, CT)作为一种无创的检查方式, 能准确的反映活体结肠癌组织葡萄糖代谢, 对结肠癌的诊断、分期、判断预后和评估疗效有其不可替代的优势, 本文就*KRAS/BRAF*突变与结肠癌糖代谢相关性的研究近况作简要概述.

1 *KRAS/BRAF*基因

*RAS*基因是由Robert Weinberg从人类膀胱肿瘤中分离的首个癌基因, 活化的*Ras*导致丝裂酶原活化蛋白激酶(mitogen-actived protein kinase, MAPK)通路的活化, 进而调控细胞的生长与分化, 目前RAS-RAF-MAPK通路了解的最为清楚[4]. *RAS*基因包括*HRAS*、*KRAS*、*NRAS*, 其中*KRAS*突变与人类表皮生长因子受体(epidermal growth factor receptor, EGFR)级联反应相关, 并且与结肠癌(colorectal cancer, CRC)和非小细胞肺癌的发生发展有关[5-7]. CRC的*KRAS*突变多位于第12、13位, 以腺癌和黏液腺癌多见[8,9]. *RAF*是*RAS*的下游基因, *RAF*激活对多种肿瘤的发生、发展产生重要影响, 如结直肠癌、胰腺癌、乳头状甲状腺癌、卵巢癌、肺癌[10-14]. *RAF*家族包括丝氨酸/苏氨酸激酶(*ARAF*、*BRAF*及*CRAF*), *RAF*突变以*BRAF*常见, *BRAF*突变常见于V600E位点[15,16]. *KRAS/BRAF*突变导致*RAS-RAF-MAPK*通路传导异常, 引起细胞过度增殖和分化而诱发肿瘤, 并对肿瘤的增殖、侵袭和转移发挥重要作用. 因此*KRAS/BRAF*突变会影响CRC的靶向治疗效果[17-19].

2 *KRAS/BRAF*基因检测与CRC的靶向治疗

结肠癌的治疗以手术为主、放化疗为辅, 而抗EGFR靶向治疗是目前的研究热点. 研究[20]表明, 西妥昔单抗可尝试作为一线药辅助治疗CRC, 并可增加*KRAS*基因野生型CRC的化疗效果, 然而对于*KRAS*突变型CRC, 目前还没有疗效较好的靶向药物[21], 2016版美国国立综合癌症网络指南推荐对于初始可切除*RAS*野生型转移性结直肠癌(metastatic colorectal cancer, mCRC)术前使用新辅助化疗. 文献[22]报道*BRAF*基因的突变率为23%, 与*KRAS*基因突变相比, *BRAF*基因突变常见于尚未发生远处转移的结肠癌, 以Ⅱ、Ⅲ期CRC患者多见, *BRAF*突变型CRC的恶性程度高、淋巴结转移率和

局部晚期发生率高[23]. PETACC-3研究检测了1404例Ⅱ、Ⅲ期结肠癌患者的*KRAS/BRAF*突变结果显示, *KRAS/BRAF*突变型患者的总生存率比野生型患者差. 故*KRAS/BRAF*基因检测对于评估抗EGFR抗体生物靶向治疗的选择及其远期疗效评估具有指导意义[24-27], 然而*KRAS/BRAF*基因检测除了与*KRAS/BRAF*突变的异质性[28,29]相关外, 还与受检标本密切相关, 而用于*KRAS/BRAF*基因检测的标本源于活检或手术, 且转移性CRC的检测样本不容易获取. 此外组织切片的目标DNA含量较低对*KRAS/BRAF*基因检测结果亦有重要影响. 因此, 能有效反映CRC活体组织*KRAS/BRAF*基因状态的无创检查对CRC靶向治疗具有重要价值, 研究[30,31]表明结肠癌^{18}F-FDG的摄取及*KRAS/BRAF*的状态明显相关, 这表明*KRAS/BRAF*突变与结肠癌糖代谢密切相关.

3 结肠癌PET/CT显像与*KRAS/BRAF*突变

PET/CT显像作为一种无创的检查手段, 能更好从形态学和功能学为疾病诊断提供重要信息, 已被广泛用于肿瘤的诊断、监测、分期、再分期以及疗效评估[32,33]. 正电子核素^{18}F-FDG是PET/CT显像常用的显像剂, 能准确地从分子水平上反映CRC葡萄糖代谢. 文献[34]报道^{18}F-FDG-PET/CT显像对CRC转移灶的术前评估和术后随访具有重要价值, 可以减少无意义的开腹手术, 有助于发现隐匿的转移灶并制定相应手术范围, 为根治性切除提供依据. ^{18}F-FDG-PET/CT显像常用的观察指标是最大标准化摄取值(maximum standard uptake value, SUVmax), SUVmax的高低主要与细胞膜表面的葡萄糖转运体(glucose transporter, GLUT)数量及己糖激酶有关. 肿瘤细胞增殖迅速, 通过加强糖酵解来增加能量供给, 即沃伯格效应(Warburg effect)[35]. 肿瘤细胞GLUT-1的过度表达可以促进葡萄糖的吸收, 为沃伯格效应提供了大量能量底物. GLUT-1最早从人红细胞膜中提取的葡萄糖转运蛋白, 是葡萄糖转运蛋白的亚型之一, 其广泛分布于所有组织的细胞膜, 是转运葡萄糖的主要载体. 研究[36-39]表明GLUT-1在多种肿瘤过度表达, 如结直肠癌、肝癌、胰腺癌、食管癌、肺癌、乳腺癌、卵巢癌、肾癌等. GLUT-1表达受抑制时, 通过介导EGFR、MAPK信号途径导致细胞分化减少、葡萄糖摄取减低、细胞运动和侵袭减弱[40]. 当EGFR的配体受抑制时, GLUT-1的表达及葡萄糖摄取均降低[41]. 研究[42]表明缺氧、*KRAS*突变与GLUT-1表达存在协同交互作用: 结肠癌细胞系在缺氧状态下, *KRAS*突变通过PI3K信号路径使缺氧耐受因子-1α的表达增加. 缺氧同样会导致*KRAS*突变增加, 这表明缺氧与KRAS突变可能存在反馈机制[43]. 此外, 缺氧通过介导缺氧耐受因子-1α增加GLUT-1表达[44], 亦有研究[45,46]表明*KRAS*突变型CRC细胞在含氧量正常的情况下通过GLUT-1表达上调来增加18F-FDG的摄取. 研究[30]表明GLUT-1的表达与^{18}F-FDG的摄取及*KRAS/BRAF*的状态明显相关而与己糖激酶Ⅱ无明显相关. 此外, 有学者通过对结直肠癌细胞系进行体外研究[47]表明肿瘤细胞的低糖环境促使*KRAS*、*BRAF*突变进而促进GLUT-1表达及葡萄糖摄取, 结肠癌细胞^{18}F-FDG-PET/CT显像检出癌前病变进展的时间与*KRAS*或*BRAF*突变的时间一致, 这表明结肠癌细胞葡萄糖摄取与*KRAS*或*BRAF*突变存在相关性. 曾有学者对50例行PET/CT检查的CRC患者进行回顾性分析[30], 他们发现与*KRAS/BRAF*野生型相比, *KRAS/BRAF*突变型患者原发灶SUVmax更高, 当以13或14作为SUVmax的临界值时, ^{18}F-FDG-PET/CT显像预测结直肠癌*KRAS/BRAF*突变的准确率可达75%. Lee等[48]研究表明SUVmax及SUV_{peak}可以预测*KRAS*突变及淋巴结转移, 但受到炎症的影响. 研究[31]表明SUVmax及TW40%(40% threshold level for maximal uptake of tumor width)可以预测*KRAS*突变, SUVmax预测结肠癌突变较准确而TW40%预测直肠癌突变较准确. Cho等[49]研究表明较高的FDG指数(SUVmax、总病灶糖酵解)可以预测*KRAS*突变状态. Kawada等[50]研究表明转移性结直肠癌FDG摄取与*KRAS*突变状态有关, ^{18}F-FDG-PET/CT显像有助于预测转移性结直肠癌*KRAS*突变状态并对其治疗决策产生影响. 亦有文献[51]报道^{18}F-FDG-PET/CT显像可以反映结直肠癌及非小细胞肺癌*KRAS*突变状态. 综上, *KRAS/BRAF*突变可通过GLUT-1影响活体结肠癌组织SUVmax, ^{18}F-FDG-PET/CT有可能成为反映活体组织结肠癌突变状态有效的无创检查方式, 从而为结肠癌的治疗和预后提供重要参考.

相关报道

有学者通过对结直肠癌细胞系进行体外研究表明肿瘤细胞的低糖环境促使*KRAS*、*BRAF*突变进而促进葡萄糖转运体-1表达及葡萄糖摄取, 结肠癌细胞^{18}F-FDG-PET/CT显像检出癌前病变进展的时间与*KRAS*或*BRAF*突变的时间一致, 这表明结肠癌细胞葡萄糖摄取与*KRAS*或*BRAF*突变存在相关性. 曾有学者对50例行PET/CT检查的CRC患者进行回顾性分析, 他们发现与*KRAS/BRAF*野生型相比, *KRAS/BRAF*突变型患者原发灶最大标准化摄取值(maximum standard uptake value, SUVmax)更高, 当以13或14作为SUVmax的临界值时, ^{18}F-FDG-PET/CT显像预测结直肠癌*KRAS/BRAF*突变的准确率可达75%.

创新盘点

本文结合近期文献, 对*KRAS/BRAF*基因背景、CRC活体组织*KRAS/BRAF*基因状态的无创检查对CRC靶向治疗必要性以及^{18}F-FDG-PET/CT反映活体组织结肠癌突变状态的机制和有效性进行了分析.

4 展望

*KRAS/BRAF*基因检测对结肠癌的治疗及判断预后具有重要意义, 肿瘤细胞微环境(低糖或低氧)与*KRAS/BRAF*突变以及FDG摄取存在明显相关性, ^{18}F-FDG-PET/CT显像作为一种无创的检查手段, 对预测结直肠癌*KRAS/BRAF*基因状态具有重要价值. 然而FDG-PET/CT显像预测结直肠癌*KRAS/BRAF*突变准确性在60%左右, 且与研究对象、实验方法有密切相关, 是否存在其他基因影响*RAS-RAF-MAPK*通路传导尚未可知, 现有研究对FDG-PET/CT显像预测结直肠癌*KRAS/BRAF*突变尚有争议, 尚需大样本研究及探索FDG-PET参数来提高FDG-PET/CT显像预测结直肠癌*KRAS/BRAF*突变的准确性, 从而为CRC的靶向治疗及预后提供重要参考. 在倡导针对肿瘤精准医疗的时代背景下, 探讨结肠癌PET/CT显像SUVmax与*KRAS/BRAF*突变状态的内在联系对于结肠癌的精准医疗具有重要意义.

5 参考文献

1 郑树, 张苏展, 黄彦钦. 结直肠癌研究30年回顾和现状. 实用肿瘤杂志 2016; 31: 2-5

2 Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, Maus MK, Antoniotti C, Langer C, Scherer SJ, Müller T, Hurwitz HI, Saltz L, Falcone A, Lenz HJ. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst* 2015; 107: pii dju427 [PMID: 25713148 DOI: 10.1093/jnci/dju427]

3 Yang J, Du XL, Li ST, Wang BY, Wu YY, Chen ZL, Lv M, Shen YW, Wang X, Dong DF, Li D, Wang F, Li EX, Yi M, Yang J. Characteristics of Differently Located Colorectal Cancers Support Proximal and Distal Classification: A Population-Based Study of 57,847 Patients. *PLoS One* 2016; 11: e0167540 [PMID: 27936129 DOI: 10.1371/journal.pone.0167540]

4 Semrad TJ, Kim EJ. Molecular testing to optimize therapeutic decision making in advanced colorectal cancer. *J Gastrointest Oncol* 2016; 7: S11-S20 [PMID: 27034809 DOI: 10.3978/j.issn.2078-6891.2015.094]

5 Xiong J, He M, Hansen K, Jackson CL, Breese V, Quddus MR, Sung CJ, Lomme MM, Lawrence WD. The clinical significance of K-ras mutation in endometrial "surface epithelial changes" and their associated endometrial adenocarcinoma. *Gynecol Oncol* 2016; 142: 163-168 [PMID: 27154241 DOI: 10.1016/j.ygyno.2016.05.001]

6 Marabese M, Ganzinelli M, Garassino MC, Shepherd FA, Piva S, Caiola E, Macerelli M, Bettini A, Lauricella C, Floriani I, Farina G, Longo F, Bonomi L, Fabbri MA, Veronese S, Marsoni S, Broggini M, Rulli E. KRAS mutations affect prognosis of non-small-cell lung cancer patients treated with first-line platinum containing chemotherapy. *Oncotarget* 2015; 6: 34014-34022 [PMID: 26416458 DOI: 10.18632/oncotarget.5607]

7 Blumenschein GR, Smit EF, Planchard D, Kim DW, Cadranel J, De Pas T, Dunphy F, Udud K, Ahn MJ, Hanna NH, Kim JH, Mazieres J, Kim SW, Baas P, Rappold E, Redhu S, Puski A, Wu FS, Jänne PA. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC)†. *Ann Oncol* 2015; 26: 894-901 [PMID: 25722381 DOI: 10.1093/annonc/mdv072]

8 Krajnović M, Marković B, Knežević-Ušaj S, Nikolić I, Stanojević M, Nikolić V, Šiljić M, Jovanović Ćupić S, Dimitrijević B. Locally advanced rectal cancers with simultaneous occurrence of KRAS mutation and high VEGF expression show invasive characteristics. *Pathol Res Pract* 2016; 212: 598-603 [PMID: 27184911 DOI: 10.1016/j.prp.2016.02.018]

9 Lou E, D'Souza D, Nelson AC. Therapeutic Response of Metastatic Colorectal Cancer Harboring a KRAS Missense Mutation After Combination Chemotherapy With the EGFR Inhibitor Panitumumab. *J Natl Compr Canc Netw* 2017; 15: 427-432 [PMID: 28404754 DOI: 10.6004/jnccn.2017.0043]

10 Hertzman Johansson C, Egyhazi Brage S. BRAF inhibitors in cancer therapy. *Pharmacol Ther* 2014; 142: 176-182 [PMID: 24325952 DOI: 10.1016/j.pharmthera.2013.11.011]

11 Pereira AA, Rego JF, Morris V, Overman MJ, Eng C, Garrett CR, Boutin AT, Ferrarotto R, Lee M, Jiang ZQ, Hoff PM, Vauthey JN, Vilar E, Maru D, Kopetz S. Association between KRAS mutation and lung metastasis in advanced colorectal cancer. *Br J Cancer* 2015; 112: 424-428 [PMID: 25535726 DOI: 10.1038/bjc.2014.619]

12 Nakayama N, Nakayama K, Yeasmin S, Ishibashi M, Katagiri A, Iida K, Fukumoto M, Miyazaki K. KRAS or BRAF mutation status is a useful predictor of sensitivity to MEK inhibition in ovarian cancer. *Br J Cancer* 2008; 99: 2020-2028 [PMID: 19018267 DOI: 10.1038/sj.bjc.6604783]

13 Tjensvoll K, Lapin M, Buhl T, Oltedal S, Steen-Ottosen Berry K, Gilje B, Søreide JA, Javle M, Nordgård O, Smaaland R. Clinical relevance of circulating KRAS mutated DNA in plasma from patients with advanced pancreatic cancer. *Mol Oncol* 2016; 10: 635-643 [PMID: 26725968 DOI: 10.1016/j.molonc.2015.11.012]

14 Guan JL, Zhong WZ, An SJ, Yang JJ, Su J, Chen ZH, Yan HH, Chen ZY, Huang ZM, Zhang XC, Nie Q, Wu YL. KRAS mutation in patients with lung cancer: a predictor for poor prognosis but not for EGFR-TKIs or chemotherapy. *Ann Surg Oncol* 2013; 20: 1381-1388 [PMID: 23208128 DOI: 10.1245/s10434-012-2754-z]

15 Tuttle SE, Lucas JG, Bucci DM, Schlom J, Primus J. Distinguishing malignant mesothelioma from pulmonary adenocarcinoma: an immuno-histochemical approach using a panel of monoclonal antibodies. *J Surg Oncol* 1990; 45: 72-78 [PMID: 2214794 DOI: 10.1158/1078-0432.CCR-11-2246]

16 Asl JM, Almasi S, Tabatabaiefar MA. High frequency of BRAF proto-oncogene hot spot mutation V600E in cohort of colorectal cancer patients from Ahvaz City, southwest Iran. *Pak J Biol Sci* 2014; 17: 565-569 [PMID: 25911848 DOI: 10.3923/pjbs.2014.565.569]

17 De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, Kalogeras KT, Kotoula V, Papamichael D, Laurent-Puig P, Penault-Llorca F, Rougier P, Vincenzi B, Santini D, Tonini G, Cappuzzo F, Frattini M, Molinari F, Saletti P, De Dosso S, Martini M, Bardelli A, Siena S, Sartore-Bianchi A, Tabernero J, Macarulla T, Di Fiore F, Gangloff AO, Ciardiello F, Pfeiffer P, Qvortrup C, Hansen TP, Van Cutsem E, Piessevaux H, Lambrechts D, Delorenzi M, Tejpar S. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010; 11: 753-762 [PMID: 20619739 DOI: 10.1016/S1470-2045(10)70130-3]

18 Therkildsen C, Bergmann TK, Henrichsen-Schnack T, Ladelund S, Nilbert M. The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis. *Acta Oncol* 2014; 53: 852-864 [PMID: 24666267 DOI: 10.3109/0284186X.2014.895036]

19 Chen J, Guo F, Shi X, Zhang L, Zhang A, Jin H, He Y. BRAF V600E mutation and KRAS codon 13 mutations predict poor survival in Chinese colorectal cancer patients. *BMC Cancer* 2014; 14: 802 [PMID: 25367198 DOI: 10.1186/1471-2407-14-802]

20 Chen KH, Shao YY, Chen HM, Lin YL, Lin ZZ, Lai MS, Cheng AL, Yeh KH. Primary tumor site is a useful predictor of cetuximab efficacy in the third-line or salvage treatment of KRAS wild-type (exon 2 non-mutant) metastatic colorectal cancer: a nationwide cohort study. *BMC Cancer* 2016; 16: 327 [PMID: 27221731 DOI: 10.1186/s12885-016-2358-2]

21 Wang J, Hu K, Guo J, Cheng F, Lv J, Jiang W, Lu W, Liu J, Pang X, Liu M. Suppression of KRas-mutant cancer through the combined inhibition of KRAS with PLK1 and ROCK. *Nat Commun* 2016; 7: 11363 [PMID: 27193833 DOI: 10.1038/ncomms11363]

22 Birgisson H, Edlund K, Wallin U, Påhlman L, Kultima HG, Mayrhofer M, Micke P, Isaksson A, Botling J, Glimelius B, Sundström M. Microsatellite instability and mutations in BRAF and KRAS are significant predictors of disseminated disease in colon cancer. *BMC Cancer* 2015; 15: 125 [PMID: 25884297 DOI: 10.1186/s12885-015-1144-x]

23 Summers MG, Smith CG, Maughan TS, Kaplan R, Escott-Price V, Cheadle JP. BRAF and NRAS Locus-Specific Variants Have Different Outcomes on Survival to Colorectal Cancer. *Clin Cancer Res* 2017; 23: 2742-2749 [PMID: 27815357 DOI: 10.1158/1078-0432.CCR-16-1541]

24 Health Quality Ontario. KRAS Testing for Anti-EGFR Therapy in Advanced Colorectal Cancer: An Evidence-Based and Economic Analysis. *Ont Health Technol Assess Ser* 2010; 10: 1-49 [PMID: 23074403]

25 Soeda H, Shimodaira H, Watanabe M, Suzuki T, Gamoh M, Mori T, Komine K, Iwama N, Kato S, Ishioka C. Clinical usefulness of KRAS, BRAF, and PIK3CA mutations as predictive markers of cetuximab efficacy in irinotecan- and oxaliplatin-refractory Japanese patients with metastatic colorectal cancer. *Int J Clin Oncol* 2013; 18: 670-677 [PMID: 22638623 DOI: 10.1007/s10147-012-0422-8]

26 Barone C, Pinto C, Normanno N, Capussotti L, Cognetti F, Falcone A, Mantovani L. KRAS early testing: consensus initiative and cost-effectiveness evaluation for metastatic colorectal patients in an Italian setting. *PLoS One* 2014; 9: e85897 [PMID: 24465771 DOI: 10.1371/journal.pone.0085897]

27 Herr R, Brummer T. BRAF inhibitors in colorectal cancer: Toward a differentiation therapy? *Mol Cell Oncol* 2015; 2: e1002709 [PMID: 27308494 DOI: 10.1080/23723556.2014.1002709]

28 Albanese I, Scibetta AG, Migliavacca M, Russo A, Bazan V, Tomasino RM, Colomba P, Tagliavia M, La Farina M. Heterogeneity within and between primary colorectal carcinomas and matched metastases as revealed by analysis of Ki-ras and p53 mutations. *Biochem Biophys Res Commun* 2004; 325: 784-791 [PMID: 15541358 DOI: 10.1016/j.bbrc.2004.10.111]

29 Molinari F, Martin V, Saletti P, De Dosso S, Spitale A, Camponovo A, Bordoni A, Crippa S, Mazzucchelli L, Frattini M. Differing deregulation of EGFR and downstream proteins in primary colorectal cancer and related metastatic sites may be clinically relevant. *Br J Cancer* 2009; 100: 1087-1094 [PMID: 19293803 DOI: 10.1038/sj.bjc.6604848]

30 Kawada K, Nakamoto Y, Kawada M, Hida K, Matsumoto T, Murakami T, Hasegawa S, Togashi K, Sakai Y. Relationship between 18F-fluorodeoxyglucose accumulation and KRAS/BRAF mutations in colorectal cancer. *Clin Cancer Res* 2012; 18: 1696-1703 [PMID: 22282467 DOI: 10.1158/1078-0432.CCR-11-1909]

31 Chen SW, Chiang HC, Chen WT, Hsieh TC, Yen KY, Chiang SF, Kao CH. Correlation between PET/CT parameters and KRAS expression in colorectal cancer. *Clin Nucl Med* 2014; 39: 685-689 [PMID: 24978328 DOI: 10.1097/RLU.0000000000000481]

32 Engelmann BE, Loft A, Kjær A, Nielsen HJ, Berthelsen AK, Binderup T, Brinch K, Brünner N, Gerds TA, Høyer-Hansen G, Kristensen MH, Kurt EY, Latocha JE, Lindblom G, Sloth C, Højgaard L. Positron emission tomography/computed tomography for optimized colon cancer staging and follow up. *Scand J Gastroenterol* 2014; 49: 191-201 [PMID: 24286594 DOI: 10.3109/00365521.2013.863967]

33 Engelmann BE, Loft A, Kjær A, Nielsen HJ, Gerds TA, Benzon EV, Brünner N, Christensen IJ, Hansson SH, Holländer NH, Kristensen MH, Löfgren J, Markova E, Sloth C, Højgaard L. Positron emission tomography/computed tomography and biomarkers for early treatment response evaluation in metastatic colon cancer. *Oncologist* 2014; 19: 164-172 [PMID: 24451199 DOI: 10.1634/theoncologist.2013-0229]

34 Briggs RH, Chowdhury FU, Lodge JP, Scarsbrook AF. Clinical impact of FDG PET-CT in patients

■应用要点

*KRAS/BRAF*基因检测对结肠癌靶向治疗及判断预后具有重要意义，有文献报道^{18}F-FDG-PET/CT作为一种无创的检查方式，能预测结肠癌*KRAS/BRAF*突变状态，从而为临床提供重要参考.

同行评价

本文内容较为全面、深入，立意新颖、语言精练、层次分明、有逻辑性，对临床工作有很好的指导意义.

with potentially operable metastatic colorectal cancer. *Clin Radiol* 2011; 66: 1167-1174 [PMID: 21867996 DOI: 10.1016/j.crad.2011.07.046]

35 Otto AM. Warburg effect(s)-a biographical sketch of Otto Warburg and his impacts on tumor metabolism. *Cancer Metab* 2016; 4: 5 [PMID: 26962452 DOI: 0.1186/s40170-016-0145-9]

36 Wellberg EA, Johnson S, Finlay-Schultz J, Lewis AS, Terrell KL, Sartorius CA, Abel ED, Muller WJ, Anderson SM. The glucose transporter GLUT1 is required for ErbB2-induced mammary tumorigenesis. *Breast Cancer Res* 2016; 18: 131 [PMID: 27998284 DOI: 10.1186/s13058-016-0795-0]

37 Oda Y, Aishima S, Shindo K, Fujino M, Mizuuchi Y, Hattori M, Miyazaki T, Tanaka M, Oda Y. SLC2A1/GLUT1 expression in mural nodules of intraductal papillary mucinous neoplasm of the pancreas. *Hum Pathol* 2017 Apr 12. *[Epub ahead of print]* [PMID: 28412205 DOI: 10.1016/j.humpath.2017.03.008]

38 Fan R, Hou WJ, Zhao YJ, Liu SL, Qiu XS, Wang EH, Wu GP. Overexpression of HPV16 E6/E7 mediated HIF-1α upregulation of GLUT1 expression in lung cancer cells. *Tumour Biol* 2016; 37: 4655-4663 [PMID: 26508030 DOI: 10.1007/s13277-015-4221-5]

39 Saigusa S, Toiyama Y, Tanaka K, Okugawa Y, Fujikawa H, Matsushita K, Uchida K, Inoue Y, Kusunoki M. Prognostic significance of glucose transporter-1 (GLUT1) gene expression in rectal cancer after preoperative chemoradiotherapy. *Surg Today* 2012; 42: 460-469 [PMID: 22072148 DOI: 10.1007/s00595-011-0027-2]

40 Oh S, Kim H, Nam K, Shin I. Glut1 promotes cell proliferation, migration and invasion by regulating epidermal growth factor receptor and integrin signaling in triple-negative breast cancer cells. *BMB Rep* 2017; 50: 132-137 [PMID: 27931517 DOI: 10.5483/BMBRep.2017.50.3.189]

41 Nam SO, Yotsumoto F, Miyata K, Fukagawa S, Yamada H, Kuroki M, Miyamoto S. Warburg effect regulated by amphiregulin in the development of colorectal cancer. *Cancer Med* 2015; 4: 575-587 [PMID: 25644309 DOI: 10.1002/cam4.416]

42 Kikuchi H, Pino MS, Zeng M, Shirasawa S, Chung DC. Oncogenic KRAS and BRAF differentially regulate hypoxia-inducible factor-1alpha and -2alpha in colon cancer. *Cancer Res* 2009; 69: 8499-8506 [PMID: 19843849 DOI: 10.1158/0008-5472.CAN-09-2213]

43 Wang Y, Lei F, Rong W, Zeng Q, Sun W. Positive feedback between oncogenic KRAS and HIF-1α confers drug resistance in colorectal cancer. *Onco Targets Ther* 2015; 8: 1229-1237 [PMID: 26060408 DOI: 10.2147/OTT.S80017]

44 Lee-Kong SA, Ruby JA, Chessin DB, Pucciarelli S, Shia J, Riedel ER, Nitti D, Guillem JG. Hypoxia-related proteins in patients with rectal cancer undergoing neoadjuvant combined modality therapy. *Dis Colon Rectum* 2012; 55: 990-995 [PMID: 22874607 DOI: 10.1097/DCR.0b013e31825bd80c]

45 Zhdanov AV, Dmitriev RI, Papkovsky DB. Bafilomycin A1 activates HIF-dependent signalling in human colon cancer cells via mitochondrial uncoupling. *Biosci Rep* 2012; 32: 587-595 [PMID: 22943412 DOI: 10.1042/BSR20120085]

46 Labak CM, Wang PY, Arora R, Guda MR, Asuthkar S, Tsung AJ, Velpula KK. Glucose transport: meeting the metabolic demands of cancer, and applications in glioblastoma treatment. *Am J Cancer Res* 2016; 6: 1599-1608 [PMID: 27648352]

47 Yun J, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, Schmidt K, Willson JK, Markowitz S, Zhou S, Diaz LA, Velculescu VE, Lengauer C, Kinzler KW, Vogelstein B, Papadopoulos N. Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. *Science* 2009; 325: 1555-1559 [PMID: 19661383 DOI: 10.1126/science.1174229]

48 Lee JH, Kang J, Baik SH, Lee KY, Lim BJ, Jeon TJ, Ryu YH, Sohn SK. Relationship Between 18F-Fluorodeoxyglucose Uptake and V-Ki-Ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog Mutation in Colorectal Cancer Patients: Variability Depending on C-Reactive Protein Level. *Medicine* (Baltimore) 2016; 95: e2236 [PMID: 26735530 DOI: 10.1097/MD.0000000000002236]

49 Cho A, Jo K, Hwang SH, Lee N, Jung M, Yun M, Hwang HS. Correlation between KRAS mutation and (18)F-FDG uptake in stage IV colorectal cancer. *Abdom Radiol* (NY) 2017; 42: 1621-1626 [PMID: 28161825 DOI: 10.1007/s00261-017-1054-2]

50 Kawada K, Toda K, Nakamoto Y, Iwamoto M, Hatano E, Chen F, Hasegawa S, Togashi K, Date H, Uemoto S, Sakai Y. Relationship Between 18F-FDG PET/CT Scans and KRAS Mutations in Metastatic Colorectal Cancer. *J Nucl Med* 2015; 56: 1322-1327 [PMID: 26135109 DOI: 10.2967/jnumed.115.160614]

51 Payandeh M, Shazad B, Sadeghi M, Shahbazi M. Correlation between RAS Test Results and Prognosis of Metastatic Colorectal Cancer Patients: a Report from Western Iran. *Asian Pac J Cancer Prev* 2016; 17: 1729-1732 [PMID: 27221845 DOI: 10.7314/APJCP.2016.17.4.1729]

编辑: 闫晋利 电编: 李瑞芳

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ISSN 1009-3079