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·专家论坛(专题)·

结肠癌与直肠癌生物学行为及临床治疗的差异

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[摘 要] 目前,越来越多的证据表明结肠癌和直肠癌是截然不同的疾病,无论是疾病的流行病学、解剖与组织学、分子特征、转移模式,还是临床治疗方法及疗效、预后等方面都存在许多差异,在临床治疗上也不能笼统地认为是同一种疾病。通过对CALGB/SWOG 80405、CRYSTAL、FIRE-3三大临床研究的回顾性分析发现,左、右半结肠癌使用西妥昔单抗和贝伐珠单抗的疗效存在明显差异,基于上述临床试验,2017年美国国立综合癌症网络(NCCN)首次将原发部位对治疗结肠癌决策的影响写入指南。在当前倡导精准化、个体化治疗的时代,明确结肠癌和直肠癌的发病机制、组织学差异以及临床对药物的不同反应等,不仅可以减轻患者的经济负担,而且可以为逐步实现患者的精准治疗提供最科学的依据。

[关键词] 结肠癌;直肠癌;生物学行为;临床治疗;差异
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Differences in biological behaviors and clinical treatment between colon and rectal cancers

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[Abstract] At present, more and more evidence shows that colon and rectal cancers are different diseases. There are many differences no matter in the epidemiology, anatomy and histology, molecular characteristics, transfer patterns, or clinical treatment methods, therapeutic effects and prognosis. In clinical treatment, it cann't be considered as the same disease in general. Through the retrospective analysis of the three clinical studies of CALGB/SWOG 80405, CRYSTAL, and FIRE-3, it has been found that there were significant differences in the efficacy of cetuximab and bevacizumab in left and right colon cancer. Based on the above clinical trials, the National Cancer Institute for the United States (NCCN) for the first time includes the guidelines for the impact of primary sites on the treatment of colon cancer into guidelines in 2017. In the current era of advocating precision and individualized treatment, to clarify the pathogenesis, histological differences and clinical response to drugs in colon cancer and rectal cancer, can not only reduce the economic burden of patients, but also provide the most scientific basis for the precise treatment of patients gradually.

[Key words] colon cancer; rectal cancer; biological behavior; clinical treatment; difference
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结直肠癌是最常见的恶性肿瘤之一,据2017年美国癌症协会数据统计显示,全身恶性肿瘤中结直肠癌的发生率位居第3位[1]。越来越多的研究[2-4]揭示了结肠癌和直肠癌发生发展的遗传学及分子生物学机制,回顾性分析结肠癌与直肠癌的临床特征、治

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疗及预后,不难发现结肠癌与直肠癌在流行病学、解剖与组织学、分子特征、临床治疗方法及疗效等诸多方面存在差异[5-6]。直肠癌除手术治疗外,必要时还需行放疗。晚期结直肠癌的治疗经历了单纯化疗、靶向治疗、免疫治疗及个体化治疗,总生存期(overall survival,OS)的不断延长更凸显不同部位肿瘤OS及对药物的反应方面的差异。目前肿瘤治疗进入个体化治疗的时代,对过去认为的单一疾病的结直肠癌,进行进一步分型及差异的研究,将有助于肿瘤精准医疗的开展。

1　流行病学及生活方式影响因素的差异

2011年英国国家统计中心数据[7]显示,结直肠癌中,右半结肠(升、横结肠)癌占30%,左半结肠癌占27%(其中22%为乙状结肠癌)、直肠癌占27%。近几十年来,结肠癌和直肠癌发病趋势有所变化[8],在许多西方国家,右半结肠癌在过去50年里发病率不断增加,而直肠癌在过去30年里发病率呈下降趋势。右半结肠癌多发生于女性,直肠癌多发生于男性,而左半结肠癌没有表现出明显的性别差异[9-10];总体上,年轻人结直肠癌患病率逐年升高,而老年患者有所下降,这需要进一步的研究来明确这些变化趋势的原因,并确定潜在的预防和早期检测策略[11]。

临床TNM分期是结直肠癌预后的重要因素。对于直肠癌,环周切缘(circumferential margin,CRM)对预后也有重要的影响,精准确定CRM是否阳性,对于预测患者局部复发及术后生存具有很大帮助[12-14]。左、右半结肠无论在OS上,还是根治术后局部复发时间方面具有显著差异,右半结肠均差于左半结肠[15-16]。一项回顾性分析[17]显示,在预后方面,左半结肠癌优于右半结肠癌,右半结肠癌又优于直肠癌,这与它们相应的病理学、分子生物学特征密切相关。近期的研究[18]发现,除了TNM分期、肿瘤部位等常见的预后因素外,结直肠癌免疫评分(immunoscore,IS)也是重要的预后因素,其分值的高低反映结、直肠癌免疫应答的高低,按肿瘤组织中$CD3^+$、$CD8^+$细胞数目分为5级,CD^+细胞数越多,评分越高。IS为0~4分的结直肠癌患者,其5年无病生存率(disease-free survival,DFS)分别为59%、68%、78%、83%和94%,5年OS分别为40%、44%、66%、61%和76%,均具有显著差异($P<0.01$)。

多项研究[19-21]显示,体力活动、饮食及吸烟等生活因素对直肠癌与结肠癌影响不同,体力活动能降低结肠癌的发生风险,而对直肠癌则无影响。美国国立卫生研究院(NIH)[22]对506 488名参与者进行调查问卷得出相同的结论,即体力活动、吸烟、饮食等生活因素对结肠癌的影响作用超过了直肠癌,通过健康生活方式可预防结肠癌,而对预防直肠癌作用不大,但心理因素对于结肠癌与直肠癌的发生发展均有密切联系[23]。低剂量的阿司匹林能减少结直肠癌转移、复发和死亡的风险,其可改善肿瘤细胞微环境,提高免疫应答及提高T细胞对肿瘤细胞的免疫杀伤作用[24-26]。

2　解剖和组织学的差异

结肠癌以脾曲为界,分为左半结肠癌、右半结肠癌。多项研究[27-28]显示,左半结肠癌和右半结肠癌的生物学行为及预后存在较大差异。结肠与直肠的部位不同,其微生物菌落也不相同,并且微生物菌群在肿瘤的发生发展中也起一定作用[29]。结肠起源于中肠和后肠,而直肠起源于泄殖腔。直肠为左半结肠的直接延续,其长度约15 cm,高中位的直肠癌位于腹膜反折以上,手术操作空间较大,且解剖清晰,可完整切除直肠系膜,预后较好;低位直肠在盆腔内,手术空间狭小,直肠全系膜切除术(total mesorectal excision,TME)不能很好地实施,容易使癌细胞残留,进而影响预后[30]。

结直肠癌组织学上分为腺癌、黏液腺癌及印戒细胞癌3种。其中,黏液腺癌及印戒细胞癌多发生于右半结肠(占45%),较少见于左半结肠及直肠(占20%);腺癌常转移至肝,黏液腺癌及印戒细胞癌更倾向转移至骨、腹膜及其他部位[31]。

3　分子特征的差异

目前研究[2-4]发现,结直肠癌的发生发展可归纳为3种表观遗传学不稳定性:(1)染色体不稳定性(chromosome instability,CIN),80%~85%的结直肠癌发生与其有关,多发生在左半结肠和直肠,组织高分化、黏液性成分少。CIN多为染色体杂合性缺失和非整数倍体。多种基因参与,如*KRAS*、*PIK3CA*癌基因的激活,*APC*、*P53*等抑癌基因失活,使发生正常黏膜—腺瘤—癌的逐渐演变;(2)微卫星不稳定性(microsatellite instability,MSI),由于错配修复基因(mis-match repair,*MMR*)的缺陷导致,也可由体细胞突变造成,其在结直肠癌发生发展中占的比例最小(10%~15%),多发生在右半结肠,较少发生在直肠,多为黏液腺癌及印戒细胞癌,淋巴细胞浸润、组织分化差,染色体多为双倍体,参与的基因主要为*MLH1*、*MSH2*、*MSH6*、*PMS2*等;(3)CpG岛甲基化表型(CpG island methylator phenotype,CIMP),其在结直肠癌的发生发展中占有较高的比例(约40%)。CIMP多发生在右半结肠,多见于女性,其组织分化

差,有较多的BRAF突变,导致肿瘤对EGFR抑制剂拮抗。有多项研究[32]发现,MSI与CIMP发生率密切相关,而CIN与CIMP无相关性。

林奇综合征(Lynch syndrome)和家族性腺瘤性息肉病(familial adenomatous polyposis,FAP)是两个因种系突变导致的的家族性疾病,两者的发病机制不同,好发部位也不同。林奇综合征与MSI有关(通常为*MLH1*和*MSH2*),55%的肿瘤位于右半结肠,15%位于直肠。*FAP*与*APC*抑癌基因突变有关,60%发生在左半结肠,25%发生在直肠[33]。

从组织学和3种表观遗传学不稳定性的特点可以发现,左半结肠和直肠具有相似的特征,两者均与右半结肠有较大的差别。一项纳入1 443例结直肠癌患者的研究[34]发现,从右半结肠癌至直肠癌,*BRAF*突变、*CIMP-H*和*MSI-H*的改变逐渐下降。另一项研究[35]发现,左半结肠癌和直肠癌相比右半结肠癌有更多的*HER1*、*HER2*扩增,大量的非*BRAF*突变及EGFR信号通路的活化,这些分子的变化表现为从右半结肠至直肠逐渐过渡的状态。

由于二代测序(next-generation sequencing,NGS)快速的发展,结直肠癌基因测序的数据逐渐积累,许多研究人员致力于对结直肠癌进行基于基因水平的新的分子分型。2014年结直肠癌亚型联盟(Colorectal Cancer Subtyping Consortium,CRC-SC)成立,其纳入4 000例Ⅱ~Ⅲ期的结直肠癌,鉴定出4种结直肠癌分子亚型(colorectal cancer molecular subtypes,CMS),这些亚型在遗传学特征、临床表现、异常信号通路方面表现出差异[36-37]:CMS1型多见于MSI-H、存在过度突变、免疫活化肿瘤、富于BRAF突变,多发生于右半结肠;CMS2型多见于CIN-H、高度WNT信号通路活化、*P53*突变、*EGFR*过表达的肿瘤,多发生于左半结肠及直肠;CMS3型多见于*CIN-L*、*KRAS*和*PIK3CA*突变、中度WNT/MYC途径活化;CMS4型多见于VEGFR2/NOTCH3过表达、TGF-b活化、CIN/MSI异质性表达的间充质型肿瘤。CMS3型和CMS4型没有明显的解剖位置倾向。生存期方面,CMS2型患者预后最佳,CMS4型较差,而CMS1型和CMS3型介于中间。但由于CMS1型的患者存在较多的突变及MSI-H,导致大量淋巴细胞浸润,因此可能成为免疫治疗获益的最佳人群。

4 转移模式的差异

肠系膜静脉主要收集结肠的血流,然后回流至肝门静脉,所以结肠癌血行转移多见于肝,其次是肺、骨等其他部位。由于直肠下静脉直接回流至下腔静脉,所以直肠下段癌初发肺转移的概率较结肠癌高。有研究[38]显示,11.5%的直肠癌存在肺转移,结肠癌发生肺转移的仅占3.5%。结肠癌与直肠癌发生肝转移频度没有区别,但直肠癌相对于结肠癌增加了肺、骨转移的风险,并且在原发癌和肺转移癌中*KRAS*基因型差异为32.4%,而与其他部位转移中差异却为12.3%[31,39]。另一项研究[40]对比肠癌肝转移灶行手术切除或射频消融后复发的时间,发现直肠癌复发显著早于结肠癌。通过上述研究发现,直肠癌发生远处转移的比例较高且相对较早,并且*KRAS*基因状态与原发肿瘤的高度不一致率,预示着西妥昔单抗治疗的高耐药率。一项129例结直肠癌肺转移的回顾性分析[41]显示,直肠癌肺转移的患者行手术治疗后的OS显著短于结肠癌肺转移术后的患者($P<0.01$),两组患者的3年DFS存在相似的差异。

5 临床诊疗技术应用的差异

5.1 辅助诊断技术的差异

通过消化内镜及病理明确诊断存在肿瘤时,结肠癌和直肠癌在分期和治疗上有显著差别。直肠为大肠的末段,存在于狭窄的盆腔内,由诸多重要的组织结构(如神经、大血管、内生殖器、膀胱及骶骨等)包绕,所以直肠癌需要更积极的局部治疗,新辅助放化疗或者短程放疗后行TME是治疗局部进展直肠癌的标准治疗方案,其5年局部复发率小于10%[42-43]。术前有效地评估原发灶状态(T)、区域淋巴结(N)和手术CRM,明确局部复发风险的概率对于直肠癌新辅助治疗和手术治疗至关重要。区别于结肠癌,术前直肠超声内镜(endoscopic ultrasonography, EUS)和磁共振成像(magnetic resonance imaging,MRI)对直肠癌分期诊断非常重要。EUS能分辨出只侵犯到黏膜下层(T1)或固有肌层(T2)的肿瘤,其中T1类的肿瘤通过经肛门内镜显微手术可以取得很好的疗效[44]。

包含90项研究的Meta分析[45]显示,MRI在评估肿瘤浸润直肠壁深度方面敏感性高达94%,而且可以清晰地显示周边软组织结构。所以MRI是术前评估直肠癌非常重要的手段,例如可以区分肿瘤浸润至T2、达到浆膜下层或侵犯无腹膜覆盖的肠周围组织(T3)、肿瘤穿透腹膜脏层(T4a)及侵犯至邻近器官(T4b)的各种侵袭程度[46]。此外,MRI在预测淋巴结状态和手术CRM方面也有独特的作用,与结肠癌相比,直肠癌术前淋巴结状态对决定是否选择新辅助治疗或选择新辅助治疗的类型影响更大。84项研究的Meta分析[47]显示,由于MRI忽略了小的转移性淋巴结(<5 mm),通过MRI基于淋巴结大小的N分期的准确率为57%~85%,而直肠癌发生转移的大部分淋巴

结常<5 mm[48]。一项对42例接受TME的直肠癌患者的研究[49]显示,在盆腔MRI图像上,使用淋巴结信号异质性或者边缘不规则来定义淋巴结转移比单纯采用基于淋巴结大小定义转移的特异性和敏感性更高。所以,通过盆腔MRI判断淋巴结转移的形态学标准为:淋巴结边界不规则和(或)信号不均匀、淋巴结呈圆形并且直径≥5 mm。术前MRI对手术CRM同样有很好的预测作用。与CT相比,MRI在显示盆腔软组织结构上表现出明显优势。MRI能清晰地显示原发肿瘤和直肠系膜之间的距离,具有预测手术CRM是否为阳性的潜在价值。一项对374例直肠癌患者行MRI检查与病理学相关性多因素分析[50]显示,通过MRI检查发现肿瘤距离直肠系膜>1 mm时,手术CRM有较低的肿瘤侵犯风险,其结果与病理检查一致。MERCURY等[51]研究的5年随访结果表示,MRI能准确地评估直肠癌的手术CRM情况,通过MRI评估CRM阴性患者的5年OS和DFS显著高于CRM阳性的患者,而局部复发风险前者显著低于后者(P<0.05)。因此,通过盆腔MRI检查,能准确获得直肠癌T、N分期及CRM情况,从而判断是否可以完整切除肿瘤。

由于结肠的特殊解剖学位置,结肠癌很少进行放射治疗,但在直肠癌的术前新辅助治疗及辅助治疗中放疗往往是必不可少的,术前行放化疗有助于直肠癌降期,增加手术直肠癌R0切除率和保肛率[52],NCCN指南也推荐Ⅲ/Ⅳ直肠癌患者通过术前放疗增加保肛手术的机会[53]。

转移性结肠癌患者常因肠梗阻、肠出血、肠穿孔等并发症的发生而行姑息手术,但对于直肠癌,由于其术后发生并发症的风险较高,所以TME一般仅作为根治性手术来进行,在实施TME前应常规行胸部及腹部CT检查以排除直肠癌肺转移和肝转移的可能[54]。回顾性分析结果[55]显示,无论病理分期、患者因素及是否行新辅助治疗,术中淋巴结活检数目是直肠癌患者生存的独立预测因子,淋巴结活检数目<12个的患者OS显著低于活检数目≥12个的患者。

5.2　辅助化放疗的差异

目前,手术仍是结直肠癌治疗的主要手段,根治性手术后的高复发及转移风险仍是影响患者长期生存的关键因素。术后辅助化疗有助于降低局部复发和转移的风险,显著地改善患者的预后,同样是结直肠癌治疗的重要环节之一。结肠癌的局部复发率较低,辅助化疗的焦点主要针对于远处转移。直肠的解剖特点使得直肠癌与结肠癌存在不同,虽然手术方式的不断改进,直肠癌术后仍有较高的局部复发率,直肠癌辅助治疗在控制局部复发方面发挥着重要作用,而术后放疗联合化疗有助于控制局部复发率和减少远处转移风险[56]。目前直肠癌辅助治疗的研究热点仍集中在如何改进辅助化疗方案(药品种类、剂量、给药途径)以提高效果,以及放疗的方案(时间、次数、剂量)以增加放疗的疗效。

术后辅助治疗对于T3期以上或者任何T分期但淋巴结阳性的直肠癌、Ⅲ期以上的结肠癌患者,能延长5年的DFS和OS[57]。所以,上述的患者在术后应行6个月辅助化疗,可选择的化疗方案包括:CapeOX、FOLFOX、5-FU/LV或者单药卡培他滨[57-58]。

高危Ⅱ期的结直肠癌患者(T4期、肿瘤淋巴管血管神经侵犯、组织学分化差、肠梗阻或肠穿孔、淋巴结活检数目<12个、切缘不确定或阳性)应给予辅助化疗,选择方案同Ⅲ期患者[57,59]。对于Ⅱ期无高危因素的患者,多项临床研究[60]显示,术后辅助化疗未见明显获益,建议临床观察和随访。

T3期及以上、任何T分期但淋巴结阳性的直肠癌,如果术前未行放化疗,术后行辅助放疗有助于降低局部风险及增加3年DFS[61]。但其能否减少直肠癌肝、肺转移方面的研究甚少,与辅助化疗的组合方式也需要更多的临床试验验证。目前,越来越多的研究数据[62-63]显示,手术前接受过单纯放疗或者联合放化疗的患者,术后也应行辅助治疗。

5.3　全身化疗和靶向治疗联合用药的差异

晚期转移性结肠癌和直肠癌,目前多采用全身化疗及联合抗血管生成靶向药物或EGFR单抗治疗。对于直肠癌而言,*RAS*、*BRAF*均野生型的患者建议化疗联合EGFR单抗治疗,*RAS*或*BRAF*突变型的患者建议化疗联合贝伐珠单抗治疗,而对于结肠癌靶向药物的选择不仅取决于*RAS*、*BRAF*基因型而且还取决于原发肿瘤的位置。对CALGB/SWOG80405、CRYSTAL、FIRE-3三大临床研究的回顾性分析[64-66]表明,结直肠癌不同原发部位对选择西妥昔单抗或贝伐珠单抗进行治疗有一定影响,左、右半结肠癌使用两种靶向药的疗效获益各不相同。右半结肠癌使用贝伐珠单抗较左半结肠癌使用明显改善生存,而左半结肠癌使用EGFR单抗较右半结肠癌有更显著的获益。基于上述临床研究,2017年美国国立综合癌症网络(NCCN)首次将原发部位对治疗结肠癌决策的影响写入指南[67],EGFR单抗只适合用于左半结肠癌或直肠癌并且*RAS*为野生型的患者。除了原发部位,肿瘤微环境对药物的影响也是值得探讨的。与结肠癌相比,直肠癌常需要行放疗,使肿瘤微环境发生改变。趋化因子受体4(chemokine receptor 4,CXCR4)及其配体12(chemokine receptor ligand 12,CXCL12)多表达于肿瘤细胞及其周围组织,激活肿瘤与其周围组织之间信号转导[68];两者结合可活化下游信号,保护肿瘤细胞免受基因毒药物的破坏,促使肿瘤细胞的迁移和转移,而放疗可促进肿瘤细胞表达CXCR4及

其配体[69]。研究[70]表明,盆腔放疗后行卡培他滨等药物治疗能导致肿瘤CXCR4配体的过表达,这表明破坏肿瘤细胞与周围微环境的信号转导理论上可以使肿瘤细胞退缩。目前使用CXCR4抑制剂治疗直肠癌

5.4 免疫及靶向治疗的差异

结直肠癌免疫及靶向治疗是目前研究的热点。靶向治疗方面,口服多激酶抑制剂瑞戈非尼(regorafenib)已获中国食品药品监督管理总局(CFDA)批准用于治疗转移性结直肠癌,它打破了中国转移性结直肠癌患者在经过现有标准治疗后进展无药可用的局面,是靶向治疗的重要进展。瑞戈非尼主要基于CORRECT和CONCUR两大临床研究[72-73],与安慰剂组相比,瑞戈非尼组在中位OS及PFS均表现出显著优势,研究表明,无论患者是否用过靶向药物,瑞戈非尼均能够显著延长OS,尚未接受过靶向治疗的患者效果更好。此外,在包括突变型和野生型*KRAS*亚组患者中均表现出相似的PFS和OS获益,提示其有效性与*KRAS*基因状态无关。瑞戈非尼对左半结肠癌和右半结肠癌的疗效差异无统计学意义,其疗效不受肿瘤发生部位的影响;而单纯的EGFR抑制剂西妥昔单抗在左半结肠癌、直肠癌和右半结肠癌治疗效果的显著差异提示其不适合用于右半结肠癌患者。

免疫治疗方面,程序性死亡受体1(programmed cell death protein 1,PD-1)抑制剂包括派姆单抗(pembrolizumab)和纳武单抗(nivolumab)已推荐用于错配修复缺陷(deficient mismatch repair,dMMR)的转移性结直肠癌患者二线、三线治疗[74]。PD-1是一种重要的免疫抑制分子,当与其配体PD-L1结合时,可提供抑制信号,抑制T细胞活化及增殖,并诱导细胞凋亡。肿瘤细胞逃避T细胞摧毁的一种途径就是通过在其表面产生PD-L1,其与T细胞表面PD-1识别后,T细胞就不能发现肿瘤细胞和向其发出攻击信号,PD-1抑制剂正是通过解除肿瘤逃避免疫系统的新型免疫疗法。*MYC*能结合PD-L1的启动子直接调控PD-L1的转录起始,*MYC*基因在大多数恶性肿瘤中被激活并过表达,在结直肠癌中其表达与PD-L1表达显著相关[75]。一项41例单臂、Ⅱ期研究[76]表明,派姆单抗能够显著改善客观缓解率(ORR)并能提高PFS,dMMR结直肠癌组、错配修复完整(proficient mismatch repair,pMMR)结直肠癌组以及dMMR其他肿瘤组的ORR分别为62%、0%、60%;与pMMR结直肠癌组PFS的2.3个月比较,dMMR结直肠癌组的PFS尚未达到,差异有显著统计学意义。进一步地研究[77]显示,12种dMMR的实体瘤在使用PD-1抑制剂治疗后,53%的患者影像学疗效评估缓解,其中21%的患者为完全缓解,中位PFS及OS仍未达到。另一项关于纳武单抗的Ⅱ期、多中心研究[78]也显示,纳武单抗在dMMR结直肠癌患者中表现出较高的ORR及疾病控制率。

的Ⅰ期临床研究[71]表明,这些药物有良好的耐受性,但是否能通过抑制CXCR4提高传统治疗的疗效需要更多的数据支持。

6 结 语

综上所述,结肠癌和直肠癌在多方面存在差异,这些差异最终会影响两者的治疗和预后,单纯化疗、靶向治疗、免疫治疗及个体化治疗使结肠癌和直肠癌患者的OS显著延长,但对于该两种癌症的研究及治疗手段还是比较局限。有研究[79]认为,PD-1抑制剂的盲目使用可能会导致结直肠癌短期内暴发性进展,其发生机制目前尚不清楚,年龄可能是其影响因素之一。通过对结肠癌和直肠癌进一步精细的分子分型和肿瘤免疫机制的深入研究,将有助于为肿瘤免疫治疗筛选出最佳的适合人群,为患者提供最优化的治疗方案,从而逐步实现肿瘤的精准治疗,一定会给患者带来更大的生存获益。

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