

专栏导读:近2年来,本刊与AME Publishing Company合作创建的“国际在线”系列栏目得到广大读者的一致好评,今年本刊将继续为大家提供这一学习与争鸣园地。

目前,手术切除仍然是治疗胰腺癌的最有效方法,但由于胰腺在腹腔中位置隐秘、解剖结构复杂,同时胰腺癌手术需要切除多脏器,包括带肿瘤的胰腺、十二指肠和一部分空肠等,以及胆道、胰腺和消化道之间通道的重建,因此,胰腺手术一直是普通外科难度最高、风险最大的手术。此外,胰腺术后并发症的发生率远远高于其他普通外科手术,术后处理也是难点。希望本期国际在线推荐的述评文章能对读者有益。



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胰腺手术:演变及目前的个体化方案

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摘要

胰腺癌的手术切除是患者延长生命的唯一机会,但胰腺手术目前仍然是一种技术上的挑战,并伴有术后并发症的风险,尤其是胰瘘。现在胰瘘发生的危险因素已被人们熟知,通过预防性用药及技术上的干预有可能阻止胰瘘的发生。随着术后护理的进步及影像学手段的干预,大多数常见的并发症可以保守治疗。这篇综述也试图对胰腺术后最佳管理方式所存在的争议进行阐述。

关键词

胰腺肿瘤; 胰腺切除术; 胰瘘
中图分类号: R657.5

胰腺癌是一种少见的癌症类型,其发生率在世界范围内处于增长的过程中,原因可能与肥胖的发生率增加有关。胰腺癌在北美及欧洲发病率最高,可以排在第八的位置^[1-2]。尽管不是常见的癌症类型,但却存在这样严重的事实:诊断时患者大多处于疾病晚期阶段,并且通常是致命的,同时外科治疗相当复杂且没有适当的辅助治疗。此外,胰腺癌是在欧洲唯一一种可能在2014年增加病死率的癌症类型^[3]。在欧洲及北美其5年生存率约为6%,在因癌症死亡的疾病种类中排在第4位^[1-2]。然而在10%的早期诊断、病变局限的患者中其5年生存率可升至25%^[4-5]。

自从Kausch^[6]对壶腹癌患者完成第1台胰十二指肠切除术以来,胰腺癌的手术治疗方式有了巨大的进步。Whipple等^[7]在19世纪30年代对胰十二指肠切除术进行了改良,Priestley等^[8]在1944年报道了第1台成功的全胰腺切除术,Traverso以及Longmire在1978年实施了保留幽门的胰十二指肠

切除术^[9](表1)。尽管最初存在手术治疗后高病死率及患病率的问题^[12-13],但随着手术技术的进步、患者在大型医院的集中以及围手术期管理的进步,胰十二指肠切除术后病死率及患病率降低到可以接受的范围内。全胰腺切除术后的患病率及病死率也逐渐被人们所接受,同时长期的更好的血糖控制及外分泌不足的管理因新型胰岛素的使用及胰酶的补充而成为可能。由于对胰腺全切除术后的内分泌和外分泌不足管理的改进以及像IPMN(intraductal papillary mucinous neoplasm, 胰腺导管内乳头状黏液瘤)的新型临床疾病的发现,使得之前很少手术的疾病可以采取手术治疗,拓展了外科治疗的适应证。

尽管存在并发症,有效切除肿瘤仍是最重要的影响胰腺癌患者预后的独立因素^[14]。手术治疗仍是胰腺癌患者主要的治疗方式,并且是治愈疾病的唯一机会^[15-16]。

表1 胰十二指肠切除术的历史及演变

1909: Kausch 的两阶段手术: 先行胆囊切除术, 6个月后行胰头、幽门、十二指肠第一及第二段切除术, 并胃肠吻合、胆总管封闭及胰腺同十二指肠第三段吻合 ^[6]
1935: Whipple 的两阶段手术: 先行胃结肠吻合, 胆总管的游离结扎并行胆囊胃吻合术, 随后行十二指肠及胰头切除并胰腺残端封闭 ^[7]
1940: Whipple 将两步手术一次性完成并在1942年改良了胰十二指肠切除术 ^[10]
1946: Waugh 同 Clagett 第1次应用了胰胃吻合术 ^[11]
1978: Taverso 同 Longmire 报道了保留幽门的胰十二指肠切除术 ^[9]

1 胰十二指肠切除术的并发症

胰十二指肠切除术的手术指征包括胰头部的肿瘤, 以及壶腹部、十二指肠和远端的胆管肿瘤, 对于慢性胰腺炎的患者也可以实施, 而创伤的患者很少应用。最初胰十二指肠切除术相关的病死率可达25%, 而患病率高达60%。在最近的几十年中, 病死率有了明显的下降, 在高度专科化的医院, 目前病死率约为3%~5%^[17-19]。另一方面, 胰十二指肠切除术术后相关并发症仍较多, 患病率高达30%~60%^[20-24]。大多数常见的局部并发症有胃延迟排空(8%~45%)^[25-30]、胰瘘(2%~22%)^[20, 23-24, 30-34], 感染并发症如最常见的腹腔内脓肿(1%~17%)^[30, 35]以及出血。术后出血发生在3%~13%的患者中^[5, 17]。术后24 h内出血的原因可能为术中止血不彻底, 线结滑脱或吻合口出血; 腹膜后手术区域弥散性出血可能由潜在的凝血障碍所导致, 最常见于黄疸的患者^[36-37]。延迟出血发生于术后1~3周内, 常见的原因因为吻合瘘腐蚀腹膜后血管^[38], 其病死率为15%~58%^[39-40]。其他延迟出血的原因有假性动脉瘤及胰肠吻合出血。处理方式包括胰腺切除及重塑胰腺吻合^[36]。另外不是常见的并发症包括胆道炎、结肠瘘及胆瘘。系统的并发症以心肺及神经系统并发症为主^[34, 36]。多年以来, 由于胰瘘的发生率及病死率较高, 所以成为胰十二指肠切除术最值得注意的并发症^[33, 41-42]。然而, 由于外科技术的进步, 术后加强监护以及患者在专科医院的集中, 降低了病死率, 同时也降低了胰瘘的发生率。按照之前胰瘘的诊断标准, 其发生率达10%~29%^[43]。目前按照胰瘘国际学组的定义, 在优秀的中心医院胰瘘的发生率约为2%~10%^[30, 34, 41]。胰瘘的严重性在于其可能诱发如败血症、出血等并发症, 即使在今天, 这些情况的发生仍可能引起患者术后死亡, 导致患者长期住院并增加患者住院费用。造成胰瘘的风险因素包括几个方面(表2)。第一种情况是胰腺

相关的, 其中被广泛认可的因素是残余胰腺的质地; 许多研究报道柔软的胰腺实质其胰瘘的发生率高达25%^[42, 44-47]。胰管的直径被认为是另一个相关的因素。直径<3 mm的胰管是导致胰瘘的重要危险因素^[42, 44, 46-47]。胰瘘的发生也可以根据肿瘤位置进行预判, 如壶腹、胆道、十二指肠肿瘤及胆囊肿瘤也是胰瘘发生的危险因素^[48-49]。第二类风险因素为患者相关的, 包括男性、高龄(>70岁)^[48, 50]、心血管疾病(可能导致吻合口较差的血液供应)^[30]以及持续性黄疸^[51]。第三类风险因素为治疗相关的, 包括胰腺消化道吻合的类型、生长抑素的使用、外科医生的经验及术中失血情况^[20-21, 23-24, 30, 43-47, 52]。

表2 胰瘘的风险因素

胰腺相关: 柔软的胰腺质地; 胰管管径小; 壶腹、十二指肠、胆囊及胆管肿瘤
患者相关: 男性; 年龄>70岁; 心血管疾病; 持续性黄疸
治疗相关: 胰腺吻合类型; 生长抑素的使用; 外科医生的经验; 术中失血

2 并发症的预防

这些年来, 许多研究目标在于如何减少胰瘘的发生(表3)。他们发现生长抑素的应用、胰管支架以及胰腺封闭有助于减少胰瘘的发生率。此外, 吻合方式的不同, 如胰胃吻合、胰空肠吻合以及不同的胰空肠吻合技术都可能影响胰瘘的发生率(表4)。

2.1 生长抑素及其类似物

奥曲肽是一种合成的长效生长抑素类似物, 可以强效的抑制胰腺内外分泌, 对胃肠分泌也有作用。生长抑素及其类似物在术后预防性使用, 原因在于减少胰腺分泌有助于阻止胰瘘的发生。许多研究生长抑素在阻止胰瘘方面的优势, 但结果并不一致^[68]。Connor等^[69]对10篇这方面研究的文献进行Meta分析, 结果显示, 应用生长

抑素或其类似物可以降低痿的形成、胰腺特殊并发症及总体的患病率, 而吻合口破裂的发生及病死率并没有下降。Cochrane数据库系统性回顾了2013年21个试验中2 348个患者的情况, 结论为: 生长抑素或其类似物组与安慰剂组(或无用药组)相比在术后病死率、再手术率及住院时间上

无显著差别。在生长抑素类似物组, 胰痿的发生率降低, 患者的整体术后并发症数量也降低。另一方面, 当患者出现明显的胰痿时, 两组患者并无区别。基于现在的临床证据, 生长抑素及其类似物仍被推荐胰腺术后应用^[70]。

表3 胰腺手术相关试验

变量	作者	患者例数 (n)	胰痿 (%)
应用生长抑素或类似物同未使用者的比较	Büchler, 等 1992 ^[53]	125 (生长抑素) vs. 121 (控制组)	17.6 vs. 38
	Friess, 等 1995 ^[54]	122 vs. 125	12 vs. 28
	Yeo, 等 2000 ^[55]	104 vs. 107	11 vs. 9
	Sarr, 等 2003 ^[56]	135 vs. 140	24 vs. 23
	Suc, 等 2004 ^[57]	122 vs. 108	17 vs. 19
胰胃吻合(PG)同胰空肠吻合(PJ)的比较	Yeo, 等 1995 ^[58]	73 (PG) vs. 72 (PJ)	12 vs. 11
	Duffas, 等 2005 ^[59]	81 vs. 68	16 vs. 20
	Bassi, 等 2005 ^[60]	69 vs. 82	13 vs. 16
放置支架同未放置支架的比较	Winter, 等 2006 ^[61]	115 (支架组) vs. 119 (无支架组)	11.3 vs. 7.6
	Poon, 等 2007 ^[62]	60 vs. 60	6.7 vs. 20
	Pessaux, 等 2011 ^[63]	77 vs. 81	26 vs. 42
不同吻合技术的结果比较	Marcus, 等 1995 ^[64]	68 (管-黏膜) vs. 18 (套入式)	4.4 vs. 5.5
	Bassi, 等 2003 ^[65]	144 (管-黏膜) vs. (套入式)	13 vs. 15
	Berger, 等 2009 ^[66]	97 (管-黏膜) vs. 100 (套入式)	24 vs. 12
	Peng, 等 2007 ^[67]	106 (捆绑式) vs. 111 (套入式)	0 vs. 7.2

表4 胰痿的解决方案

1. 应用生长抑素 & 类似物
2. 胰胃吻合术
3. 捆绑或套入式胰空肠吻合术
4. 胰管支架
5. 胰管封闭
6. 全胰腺切除

2.2 管道支架

内部吻合口支架可以使胰液从吻合口处转流, 使得更容易的缝合减少医源性管道闭塞的风险。它的缺点是支架移动或闭塞造成胰痿。关于内部支架没有足够的研究, 并且这些研究结果是矛盾的^[71-72]。Winter等^[61]的研究包含234个患者, 结果认为内部管道支架并没有减少胰痿的发生率或严重性: 放置内部支架的患者胰痿的发生率为11.3%, 而未放置组为7.6%。外部支架有可能使胰液从胰空肠吻合处完全转流, 从而阻止胆汁将胰酶活化。Poon等^[62]在1个120例患者的研究中发现应用外部支架组胰痿发生率明显降低(6.7%), 而未放置组为20%。在Pessaux的预期的多中心随机试验中, 放置支架组在术后胰痿高危的患者中(胰腺质地柔软及无扩张胰管)降低了胰痿的发

生率(26% vs. 42%)、患病率及胃延迟排空的发生率^[63]。Cochrane数据库系统性回顾了2013年应用胰腺支架(包含内外支架)656名患者的在预防术后胰痿发生的效果, 结果显示: 无论内部或外部支架与胰痿的发生、再手术率、住院时间、整体并发症及院内死亡率相关性方面无统计学意义。在随后的分析中, 其发现外部支架的使用与较低的胰痿发生率、并发症发生率及较短的住院时间相关。这篇综述^[73]认为外部支架可能有作用, 但仍需进一步的研究。

2.3 胰空肠吻合技术

自从1942年Whipple通过实施胰空肠吻合代替残余胰腺封闭完成改良胰十二指肠切除术以来, 这种方式成为最常见的胰消化道重建方式。这些年来, 各种进一步的改良方式不断出现。例如空肠肠袢置于结肠前、结肠后或肠系膜后式, 以及孤立的Roux袢胰空肠吻合术。这些吻合可以是胰腺残端套入式与空肠的端-端吻合及存在或不存在管-黏膜缝合的端-侧吻合(图1)^[47, 65, 74-75]。2002年, Poon等^[49]比较了管-黏膜与套入式吻合, 结果发现管-黏膜吻合更加安全。2013年, Bai等^[76]进行了一项随机控制试验的Meta分析来比较

管-黏膜吻合及胰空肠套入式吻合。结果显示两种技术之间胰痿的发生率、病死率、患病率,再手术情况及患者住院时间是相似的。Berger等^[66-67]描述捆绑式胰空肠吻合技术,胰痿发生率为0%。进一步经证实的结果表明捆绑式胰空肠吻合技术与

端-端胰空肠吻合技术比较,降低了术后胰痿的发生率、病死率、患病率及缩短了住院时间。然而多名学者^[42, 64]报道捆绑式及套入式胰空肠吻合技术在胰腺质地柔软及小径胰管的患者中有更好的结果。

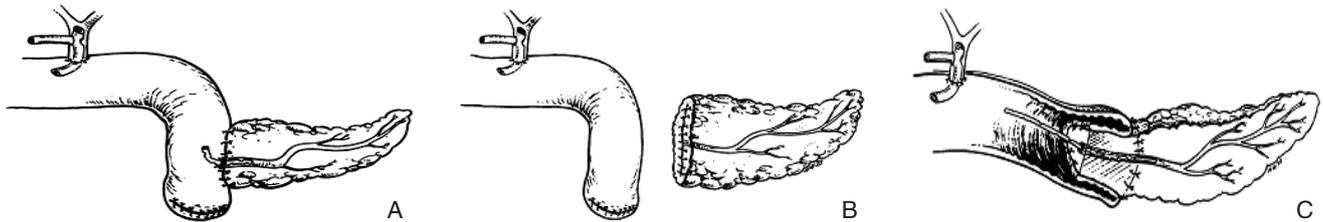


图1 胰十二指肠切除术不同的吻合方式 A: 端-侧胰空肠吻合; B: 胰腺残端缝合; C: 端-端胰空肠套入式吻合

2.4 胰腺吻合的类型

1946年, Waugh等^[11]在临床上第1次实施了胰胃吻合(图2)。这种吻合有几个优势:胰胃距离接近使得可以无张力吻合,充足的血液供应加速吻合口的生长,胃内酸度抑制胰酶的活性,同时由于缺乏肠激酶而阻止了胰蛋白酶原向胰蛋白酶转化,从而阻止了胰酶的活性,减少了因胰痿造成自我消化的风险^[78]。Yeo等^[58]第1次进行了1项比较胰空肠吻合与胰胃吻合的随即预期试验,但这项研究并没有发现两种方法在胰痿发生率上的明显不同。Duffas等^[59-60]在比较研究中,胰痿发生率、术后并发症及病死率方面也没有发现统计学差异。在2014年Menahem等^[79]发表了1篇7项随机控制试验的meta分析,其中包括胰十二指肠切除术后的562名胰胃吻合患者及559名胰空肠吻合患者。结果显示:胰胃吻合组的胰痿率明显低于胰空肠组(11.2% vs. 18.7%),胆痿的发生率也明显低于胰空肠组(2% vs. 4.8%)。Liu等^[80]的研究同样关注于比较病死率、患病率、住院时间、再手术、出血及腹腔积液情况。结果显示:胰胃吻合组不仅降低了胰痿及胆痿的发生率,同时可以减少患者腹腔积液的发生及缩短住院时间。

2.5 胰管封闭

1935年, Whipple第1次报道了胰十二指肠切除术未行胰腺消化道吻合术术后的结果,因这种方式存在较高的胰痿发生率,所以他弃用了这种术式并选择胰空肠吻合作为标准手术方式。胰管如不做吻合而采取缝扎封闭的方式,则胰痿的发生率高达80%^[64, 81-82]。Tran的1项随机控制试验包括86例胰管封闭患者及83例胰空肠吻合患者,结果显示胰管封闭组存在较高的胰痿发生率

(17% vs. 5%),但是在其他术后并发症、病死率及外分泌不足等情况下并没有发现不同。在3~12个月后,胰管封闭组的糖尿病患者明显增多^[83]。主胰管应用纤维蛋白黏合的方法也被弃用^[83-84],原因在于存在较高的痿及术后糖尿病的发生率^[83, 85]。

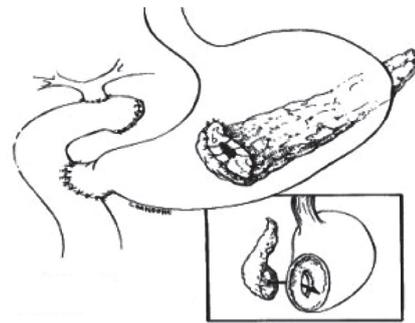


图2 胰胃吻合

3 治疗

胰十二指肠切除术术后并发症的外科干预目前仍是少见的,在大型医疗中心低于4%^[33-34]。85%~90%的胰痿患者采取液体管理、肠外营养、禁食及抗生素等保守治疗。外科干预的比例较低,也存在与高级别影像学干预手段在腹腔积液、痿及出血中的应用有关。外科干预的适应证包括临床上病情加重的患者,吻合口破裂,发展迅速的腹膜炎、腹腔脓肿、出血以及伤口裂开。如果经血管造影栓塞术术后患者病情稳定,延迟出血的患者可以保守治疗。在其他病例中,急诊外科手术有所提及^[86-87]。外科干预的类型取决于潜在的病因,方式主要有胰周引流,出血的控制以及将破裂的吻合口更换吻合类型或胰腺完整切除^[68, 78]。

残余胰腺的切除由于保守治疗及影像学干预的进步目前很少应用, 主要在患者胰腺吻合瘘并败血症或出血时应用^[88], 由于患者病情较重, 这种方式的术后病死率达38%~52%^[89-90]。

4 全胰腺切除

全胰腺切除第1次实施是由Rockey^[91]在1943年完成的, 但这名患者很快就死亡了。1944年Priestley第1次成功的实施了全胰腺切除^[8]。19世纪50年代, Ross等^[92-93]认为这种术式避免因胰腺吻合所致的病死率及患病率, 所以比胰十二指肠切除并胰空肠吻合更加安全, 因此这种术式得到广泛认可。由于Whipple手术较高的术后复发率及较差的长期生存率, 结合错误的观念(胰腺癌为多中心性疾病), 当时胰腺全切除被认为是更加彻底的手术方式^[94-95]。之后的报道揭示了这种方式的缺陷: 与胰十二指肠切除术相似或更低的长期生存率^[96], 病死率及患病率高达37%^[95-97], 以及一定会发生的糖尿病及外分泌不足。脂肪性肝炎导致的肝衰则是另一种潜在的长期并发症^[98]。没有肿瘤根治的优势, 以及糖尿病及营养不良的难以控制, 全胰腺切除在治疗胰腺肿瘤中被弃用。

近20年胰腺全切除术的应用开始逐渐增多, 原因有以下几点: 第一, 患者在大型医院的集中以及外科技术的进步使得病死率(5%)及患病率(35%)的下降^[99-101], 这些数据是与胰十二指肠切除术相当; 第二, 在于新型胰岛素的使用及更好的胰酶的补充, 外分泌的不足可以通过胰酶补充, 内分泌不足的控制可以通过加强胰岛素的方案及向患者宣教等方法解决^[102]。胰腺全切除后不仅仅表现出胰岛素的缺乏, 还存在胰高血糖素及胰多肽的不足, 这些都将导致糖尿病的发生及严重的低血糖。然而, 利用每天多次的胰岛素注射或泵入以及胰高血糖素的补充治疗, 血糖可以获得很好的控制同时HBA1c的水平也在满意范围内, 这些结果同其他原因造成的胰岛素抵抗患者相同^[99, 102-104], 以及与保留幽门的胰十二指肠切除术术后的患者情况相仿^[99-100]。第三, 在于扩大的适应证; 目前全胰腺切除术的适应证包括: 潜在恶性肿瘤的原位癌如胰腺导管内乳头状黏液瘤, 多灶性的胰岛细胞瘤, 遗传性胰腺炎以及类似的胰腺癌综合征。其他适应证包括局部高级或多中心性胰腺癌、神经内分泌肿瘤、胰腺转移肿瘤、慢性胰腺炎的终末阶段伴长期疼痛、创

伤、危险的胰腺吻合以及胰肠吻合破裂后的胰切除术^[98-99, 102]。

全胰腺切除后的病死率及患病率结果与胰十二指肠切除术术后患者并没有明显不同^[17, 33-34, 98-99], 患者的生存质量可以接受, 同时在有指征的患者中实施全胰腺切除并无其他严格的限制^[99, 101]。

5 讨论

在降低了胰十二指肠切除术术后患者30 d内病死率(5%)后, 外科医生现在开始努力降低患病率(30%~60%)^[17, 105-107]。目前的关注点在于降低胰瘘, 原因在于胰瘘被认为是造成胃延迟排空、败血症及腹腔出血等并发症的主要原因。

自从Whipple完成第1台胰十二指肠切除并胰空肠吻合术后, 外科医生开始关注于胰腺残端同消化道的重建。在专科化程度较高医院胰瘘的发生率在0~18%之间^[108], 病死率约为5%。根据国际胰瘘学会的分级方法, 将胰瘘分为A, B, C 3级, 其中C级胰瘘的发生率为2%~5%^[109-111]。C级胰瘘与败血症、出血、较高的再次手术率及延长的住院时间和较高的病死率(35%~40%)相关。目前最广泛被接受的观点是柔软的胰腺质地是胰瘘的风险因素^[112-113], 其他的3种因素包括胰管直径<3 mm, 术中的大量出血以及特定的病理位置: 壶腹部、十二指肠、胆囊以及胰岛细胞肿瘤^[111]。这个问题变成了当一个或多个胰瘘的风险因素出现时应该如何去做。有多个要素会影响手术的实施。首先, 需要保留足够的内分泌功能, 约有50%的 α 及 β 细胞应被保存^[114]。 α 及 β 细胞多存在于胰腺的尾部, 所以理论上而言, 传统的胰十二指肠切除术并不会造成胰腺的内分泌不足。当胰管堵塞, 并无胰腺吻合时, 胰腺外分泌不足是一定会发生的。应用胰管化学物质阻塞的方式的患者与胰十二指肠切除术术后的患者相比较, 除了外分泌不足以外, 糖尿病的发病率也明显增高^[83]。另一方面, 胰腺的外分泌不足也可以出现在9%~20%的Whipple术后患者中^[116-117]。原因可能包括胰管吻合的狭窄, 术后胰腺炎症或胰腺组织的纤维化^[118-119]。其他因素包括患者之前患有糖尿病或外分泌不足的状态, 患者身体的健康水平以及患者的依从性。外科医师有几种方式进行选择。第一种方式是实施胰十二指肠切除术并行胰空肠吻合, 优势在于这种吻合有较少的胰瘘发生率^[79-80]。如果胰腺质地柔软或胰管口径较小, 很多人则推荐胰十二

指肠切除术并套入式的胰空肠吻合^[67, 113]。第二种方式也是行胰十二指肠切除术,但不行吻合而做胰腺残端封闭,封闭方式可以选择主胰管结扎或其他物质阻塞主胰管。这种方式的胰痿发生率较高,但由于胰酶没有被激活,所以临床过程较平稳。最后一种选择为胰腺全切除术,可以作为对有多种风险因素患者的初始治疗,同时避免了胰痿的发生。但是由于血糖的不稳定性,甚至可能威胁生命的低血糖,患者需要密切的血糖监测以及强化的胰岛素注射方案,所以患者的依从性成为全胰腺切除术后的关键。

当外科医生面临这样一个重大问题,适当的手术管理方案有时很难决定。除了技术挑战外,患者身体健康情况、伴随疾病、胰腺病理以及预期生存期都是选择方式的关键。

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