Recent Progress in Pancreatic Cancer

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概况

- The American Cancer Society estimates that 45,220 Americans will be diagnosed with pancreatic cancer in 2013, and that38,460 will die from the disease.
- Despite decades of effort, the 5-year survival rate remains at only 5%.
- 高发年龄70-90岁
- 男女发病率相近
- 80%以上确诊时已经无法通过手术切除治愈
- R1切除术的生存获益和根治性化放疗相当

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危险因素

TABLE 1. Pancreatic Cancer Risk Factors

RISK FACTOR	RISK ESTIMATE (95% CI)
Current Cigarette Smoking	OR = 2.20 (1.71-2.83)
Past Cigarette Smoking	
1-10 years since quitting	OR = 1.64 (1.36-1.97)
15-20 years since quitting	OR = 1.12 (0.86-1.44)
Diabetes Mellitus	
<3 years	RR = 7.94 (4.70-12.55)
>10 years duration	OR = 1.51 (1.16-1.96)
BMI (>35 vs 18.9-24.9)	OR = 1.55 (1.16-2.07)
Heavy Alcohol (≥6 drinks/day)	OR = 1.46 (1.16-1.83)
Pancreatitits (>2 years)	2.71-fold (1.96-3.74)

超过1%确诊胰腺癌

超过2年的胰腺炎

BMI indicates body mass index; CI, confidence interval; OR, odds ratio; RR, relative risk.

危险因素-遗传

GENE/RISK GROUP	RISK ESTIMATE (95% CI)
General Population	1
Familial Pancreatic Cancer	
Overall	RR = 6.79 (4.54-9.75)
3 or more first-degree relatives with pancreatic cancer	RR = 17.02 (7.34-33.5)
High Penetrance	
BRCA2	RR = 3.51 (1.87-6.58)[226]
PALB2	Elevated
BRCA1	OR = 2.26 (1.26-4.06)[32]

- 胰腺癌病人亲属发生胰腺外肿瘤几率增加

  breast cancer (1.66-fold, 95%CI 1.15-2.34)

  ovarian cancer (2.05-fold, 95%CI 1.10-3.49)

  bile duct cancer (2.89-fold, 95%CI 1.04-6.39)

病理与分子生物学

- 病理类型主要是：侵袭性导管腺癌

invasive ductal adenocarcinoma

- 与以下4种基因突变关系密切：

KRAS, p16/CDKN2A, TP53 and SMAD4

- SMAD4 gene mutations in pancreatic cancer are associated with poor prognosis and with more

诊断、分期与治疗

- 胰腺癌主要表现为：体重下降、黄疸、脂肪泻、疼痛、消化不良、恶心、抑郁
- 50岁以上突发2型糖尿病、慢性胰腺炎、抑郁为新发胰腺癌的信号
- 胰腺癌确诊首选在超声内镜引导下细针穿刺活检，经皮穿刺活检有较高的腹膜播种风险
- 分期需要胰腺专用规程CT检查，必须包括三期：动脉期、动脉晚期、静脉期。MRI并不优于三期CT，超声内镜EUS可以为CT分期的补充，CT序贯PET-CT检查能明显增加对远处转移灶的特异性（87%）

诊断、分期与治疗

- 按AJCC分期指导手术：
- Resectable stages include AJCC Stages I and II, and the subset of Stage III that is defined as borderline resectable.
- The unresectable categories include the subset of Stage III that is defined as locally advanced (unresectable),and Stage IV (metastatic).
- 确诊时，65-75%病人会发生有症状的胆道梗阻，约75%的病人有疼痛症状，保守治疗前需要行内镜下支架置入术和治疗癌痛。 塑料支架与金属支架中位有效期分别为1.8个月vs3.6个月（p=0.002），并发症无差异。癌痛首选吗啡与羟考酮。

局限性可切除的判定标准：

- 无远处转移
- 无肠系膜上静脉（SMV）和门静脉被肿瘤组织围绕、变形、瘤栓形成
- 腹腔干、肝动脉、肠系膜上动脉（SMA）周围有清晰的脂肪层

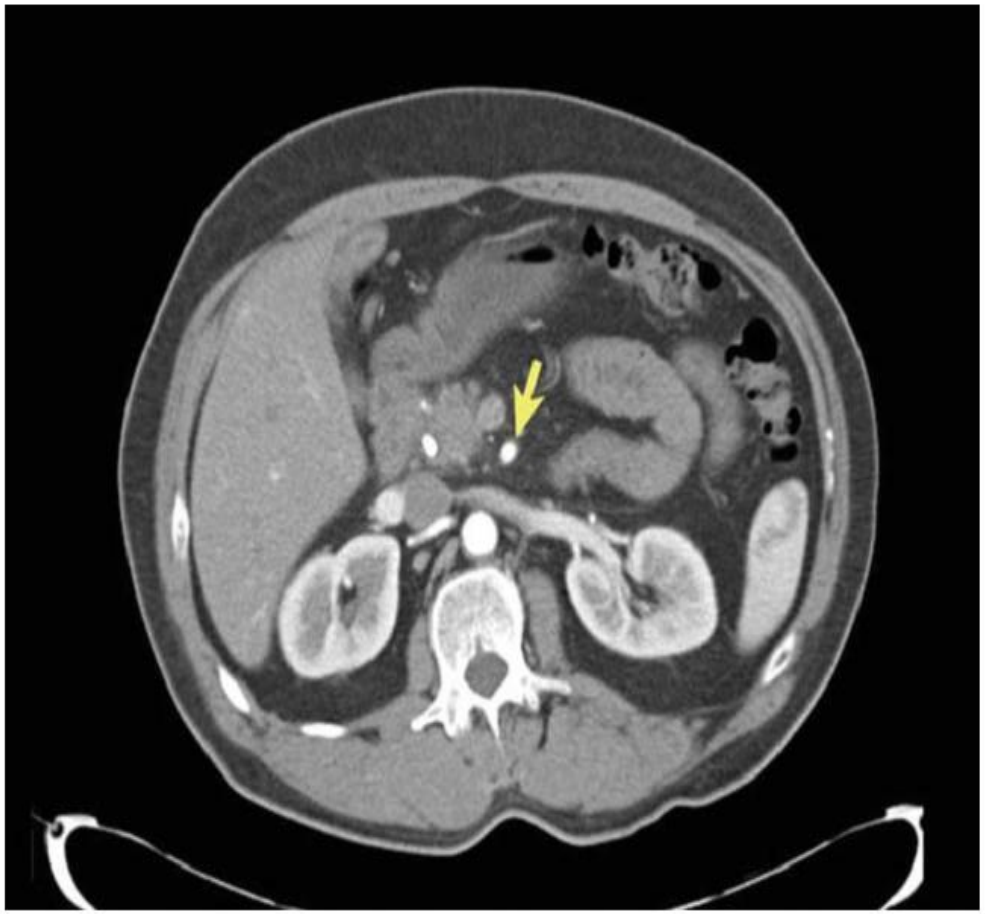
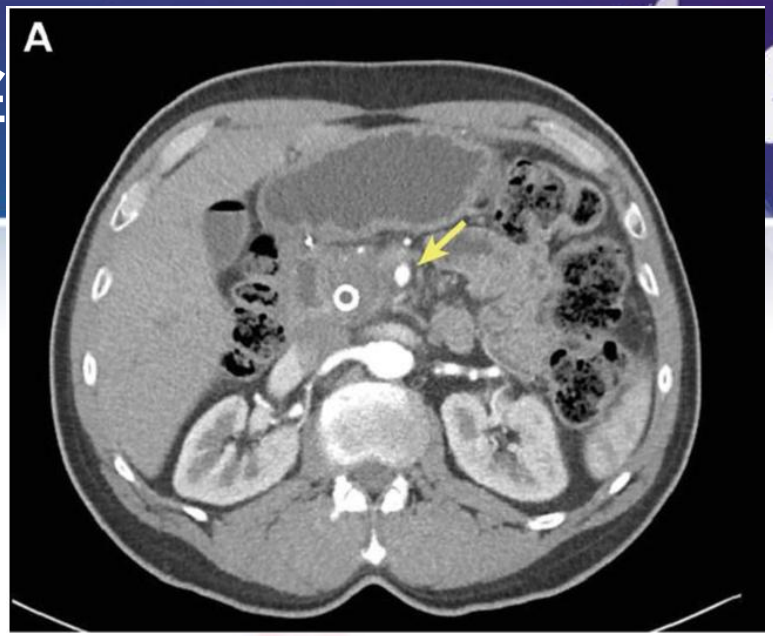
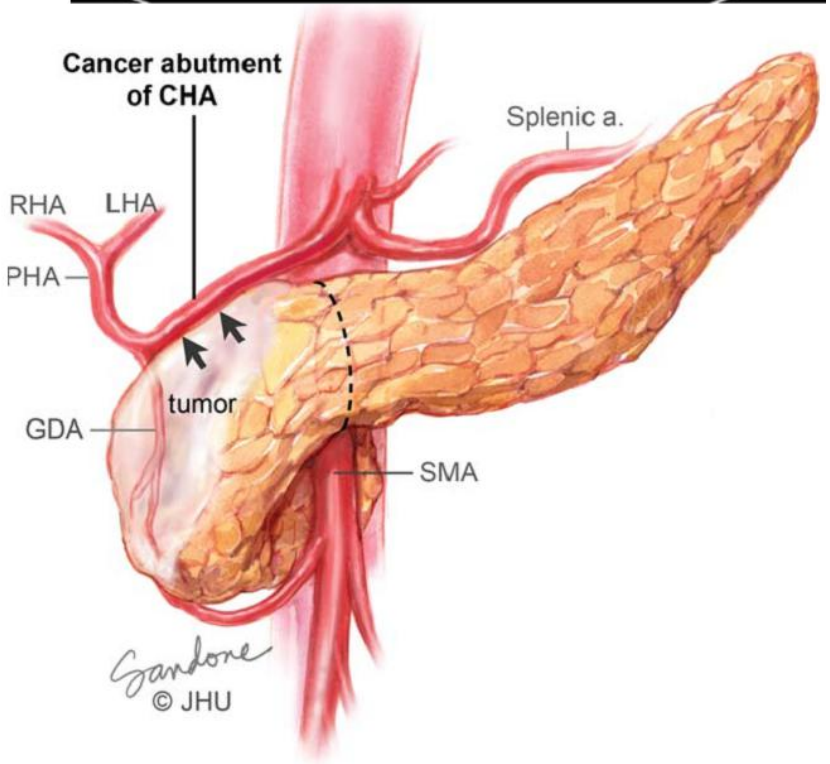


FIGURE 3. CT of Pancreatic Cancer. A resectable pancreatic cancer with a well-defined fat plane around the superior mesenteric artery (arrow).

有可能切除的判

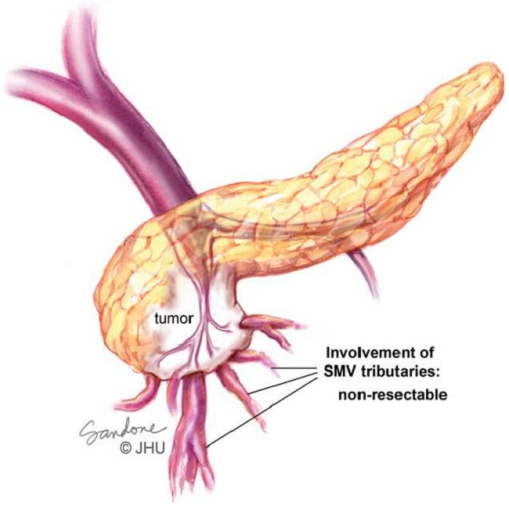
- SMV/门静脉、受累但受累静脉的近侧和远侧有合适的血管可进行安全切除及重建
- 肿瘤围绕SMA未超过180度
- 胃十二指肠动脉和肝动脉直接被包裹但未侵及腹腔干



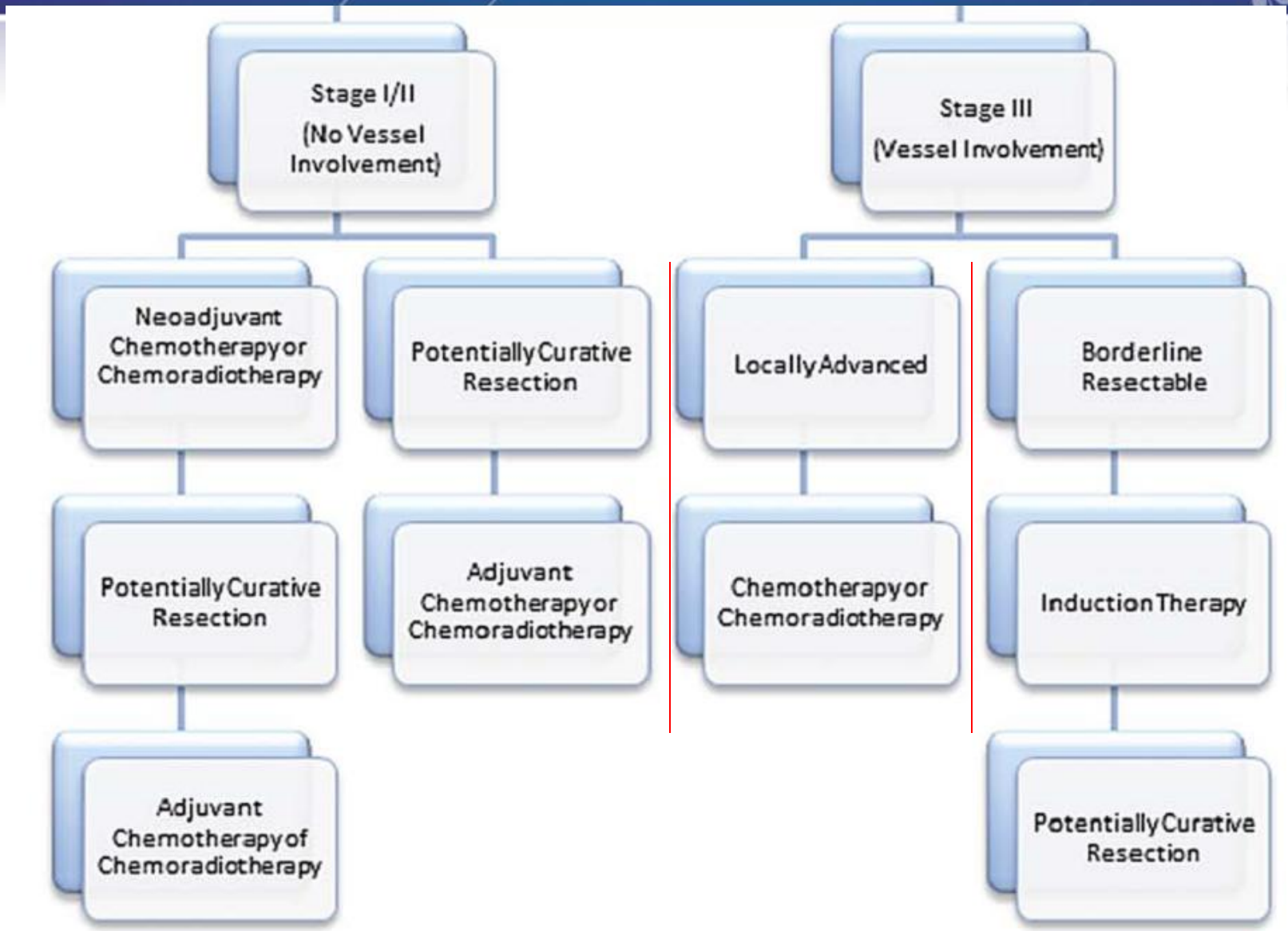


无法切除的判定标准：

- 肿瘤围绕SMA大于180度或侵犯腹腔干
- SMV/门静脉闭塞且无法重建
- 肿瘤侵犯或围绕腹主动脉



I/II期和部分III期可能切除的治疗：



I/II期和部分III期可能切除的治疗：手术

- 新辅助治疗与辅助治疗的选择：I/II期在没有手术禁忌症时选择手术+辅助化疗±放疗，III期大多数肿瘤中心选择新辅助治疗，能使15-35%病人免于不必要的手术。
- 标准术式：胰十二指肠切除术，标准术式区域外的淋巴结清扫没有生存获益，有数据提示淋巴结转移标志着肿瘤为全身性疾病
- 术后并发症高达30-45%，主要为胃排空延迟（15%）、切口感染（8%）、胰腺瘘（5%）、腹腔脓肿（5%）
- 手术死亡风险：极低手术量（0-1台/年）、低手术量（1-2台/年）、高手术量（>5台/年）比为16%：12%：4%（纽约州）
- 术后中位生存17-27月，5年OS约20%

I/II期和部分III期可能切除：新辅助治疗

- 新辅助化疗：吉西他滨或5-Fu单药、FOLFFIRINOX(5-Fu、亚叶酸钙、伊立替康、奥沙利铂)、GTX（吉西他滨、多西他赛、卡培他滨）；单药与多药联合反应率没有统计学差异

- 诱导放化疗：吉西他滨或5-Fu单药同期，放疗范围为GTV外扩1-2cm，剂量45-54Gy（1.8-2.5Gy/次）或36Gy（2.4Gy*15次）

- 约15-40%III期病人能获得切除机会，在新辅助放疗后6-8周内手术，超过8周，放疗所致纤维化会使手术难度增加

- 诱导治疗及术后仍需要根据病理结果补充2-3程辅助化疗

I/II期和部分III期可能切除的治疗：辅助治疗

- 辅助治疗开始于术后1-2月，标准方案是6个月的吉西他滨-base或5-Fu-base的化疗

- 辅助放化疗：同期6周的吉西他滨-base或5-Fu-base的化疗+放疗**45Gy**（瘤床、吻合口、胰腺周围淋巴结区），对**R1**切除的需要**5-15Gy**boost-瘤床

I/II期和部分III期可能切除的治疗：

TABLE 5. Selected Key Adjuvant Studies

STUDY (YEAR)	TREATMENT	1-y SURVIVAL (%)	2-y SURVIVAL (%)	5-y SURVIVAL (%)	DFS (mo)	MEDIAN SURVIVAL (mo)
GITSG (1985),[232] N = 43	Observe vs Chemorad	49 vs 63	15 vs 42	14 vs 4	<9 vs 16	11 vs 20 ($P = .01$)
EORTC 40891 (1999),[147] N = 218	Observe vs Chemorad	53 vs 65	23 vs 37	22 vs 25	NR	12.6 vs 17.1 (pancreas only, $P = .099$)
JHH retrospective (2006),[233] N = 452	Observe vs Chemorad	NR	32 vs 44	15.4 vs 20.4	NR	14.4 vs 21.2 ($P < .001$)
ESPAC-1 (2004),[148] N = 289	2 × 2 design	67 vs 67	38 vs 45	11 vs 29	ChemoXRT: 10.7	16.9 vs 21.6
	Observe vs Chemo				No chemoXRT: 15.2	
					Chemo: 15.3	
					No chemo: 9.4	
CONKO-1 (2007),[144] N = 354	Observe vs Chemo	72 vs 72	42 vs 47	11 vs 22	6.9 vs 13.4 ($P < .001$)	20 vs 22 ($P = .06$)
RTOG-9704 (2008),[153,234] N = 538	Gem–5-FU/XRT vs 5-FU, 5-FU/XRT	69 vs 65	35 vs 39	20 vs 20	NR	20.6 vs 16.9 ($P = .03$)
ESPAC-3 (2009),[145] N = 1030	Gem vs 5FU	70 vs 70	40 vs 40	NR	14.3 vs 14.1	23.6 vs 23
JHH and Mayo Clinic Retrospective (2010),[152] N = 1272	Observation vs Chemorad	58 vs 80	34.6 vs 44.7	16.1 vs 22.3		15.5 vs 21.1 ($P < .001$)
ACOSOG (2011),[154] N = 89	5-FU CI, IFN/cisplatin + XRT	80	60	NR	14.1	25.4
CapRI (2012),[156] N = 110	5-FU/cis/XRT + IFN followed by 5-FU vs 5-FU	85 vs 80	60 vs 55	25 vs 25	15.2 vs 11.5 ($P = .61$)	32.1 vs 28.5 ($P = .49$)

局部晚期胰腺癌的治疗

- 中位生存约8-12月，治疗前约50-60%病人需要内镜下置入支架解除梗阻性黄疸症状

- 50 to 54 Gy in 1.8 to 2.0 Gy fractions with concurrent chemotherapy (often 5-FU or gemcitabine)

- 如果患者疼痛控制不佳或伴有局部梗阻症状，直接开始化放疗可能是最佳选择。但约20%病人在完成放化疗后马上出现转移，所以没有上述肿瘤特征的病人推荐1-4周期诱导化疗后再分期，确定没有转移并一般状况好者行同期放化疗

- 2011年JCO上日本Sudo et al的一个研究：34例进展期胰腺癌，S-1同期50.4Gy放疗，followed S-1维持治疗，中位生存达到

局部晚期胰腺癌的治疗

- erlotinib与同期放疗能有35%PR率（1期研究）

- 2011年发表在JCO上的一个2期研究：

西妥昔单抗+吉西他滨+奥沙利铂 *2周期

西妥昔单抗+卡培他滨同期放化疗50.4Gy

西妥昔单抗+吉西他滨维持治疗，

中位OS为19.2个月，

1、2、4年生存率为66%、25.02%、11.3%

局部晚期胰腺癌的治疗

- IMRT和SBRT能明显降低小肠、肾、肝的剂量，SBRT在呼吸门控支持下可以仅扩3mm的边界，治疗时间明显缩短，但目前SBRT分割剂量还不明确。

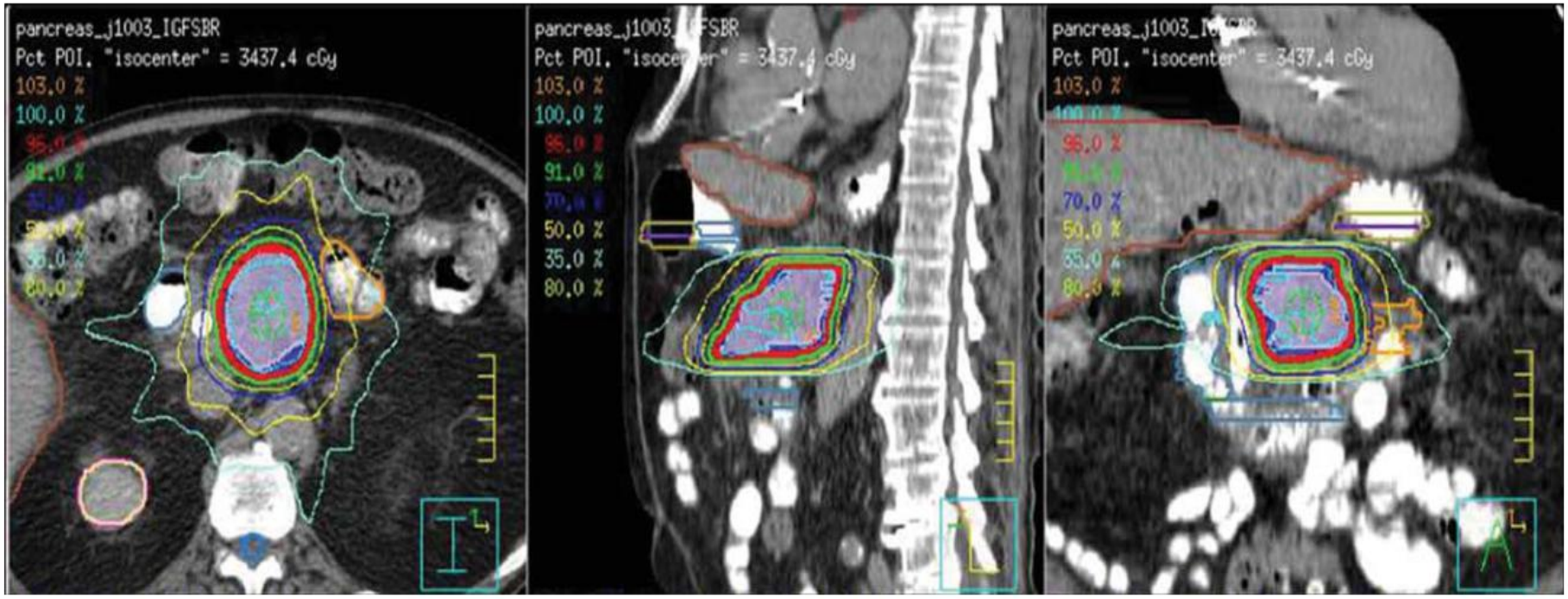


FIGURE 14. Stereotactic Body Radiation Therapy Plan Delivering 33 Gy to the Pancreatic Tumor Over 5 Treatments. Breath hold during treatment and pancreatic tumor markers (fiducials) allows for small margins (3 mm) and accurate targeting of the tumor. Notice the low dose of radiation (colored lines) to the bowel and adjacent normal structures.

转移性胰腺癌的治疗

TABLE 6. Key Metastatic Pancreatic Cancer Studies

STUDY	CHEMO	RR	MS (mo)	1-y SURVIVAL (%)
Burris et al (1997),[190] N = 126	5-FU vs Gem	NR	4.4 vs 5.6 ($P = .0025$)	2 vs 18
Rocha Lima et al (2003),[235] N = 342	Gem ± Irinotecan	4.4 vs 16	6.6 vs 6.3	22 vs 21
Heinemann et al (2003),[236] N = 195	Gem ± Cisplatin	8 vs 10.2	6 vs 7.6 ($P = .12$)	22 vs 26
Tempero et al (2003),[191] N = 92	Gem ± Gem (Fixed rate)	9.1 vs 5.9	5 vs 8 ($P = .013$)	9 vs 29
O'Reilly et al (2006),[237] N = 340	Gem ± exatecan	6.3 vs 8.2	6.2 vs 6.7 ($P = .52$)	21 vs 23
Richards et al (2004),[238] N = 565	Gem ± Pemetrexed	9.1 vs 18.3	6.3 vs 6.2 ($P = .85$)	21 vs 20 ($P = .72$)
Louvet et al (2005),[196] N = 313	Gem vs Gem (FDR+ + Oxaliplatin)	17.3 vs 26.8 ($P = .04$)	7.1 vs 9 ($P = .13$)	28 vs 35
Cunningham et al (2009),[195] N = 533	Gem ± Capecitabine	14 vs 7 ($P = .008$)	7.4 vs 6 ($P < .05$)	26 vs 19
CALGB (2009),[239] N = 259	Gem/Cis	11	6.7	
	Gem (FDR)	14	6.4	
	Gem/taxotere	12	6.4	
	Gem/Irinotecan	12	7.1	
Conroy et al (2011),[162] N = 343	Gem vs FOLFIRINOX		6.8 vs 11.1 ($P < .0001$)	17 vs 36
Moore et al (2005),[200] N = 569	Gem ± erlotinib	8.7 vs 7.9 ($P = .8$)	6.4 vs 5.9 ($P = .025$)	26 vs 20
Kindler et al (2007),[201] N = 602	Gem ± bevacizumab	13.1 vs [illegible]	6 vs 5.7	NR
Philip et al (2007),[166] N = 735	Gem ± cetuximab	14 vs 12	6 vs 6.5 ($P = .14$)	NR
Von Hoff et al (2013),[199] N = 861	Gem ± nab-paclitaxel	8.5 vs 6.7		

Cis indicates cisplatin; 5-FU, 5-fluorouracil; FDR, fixed dose rate; Gem, gemcitabine; MS, median survival; NR, not reached.

转移性胰腺癌的治疗

- FOLFIRINOX ：

  奥沙利铂85 mg/m2+亚叶酸钙 400 mg/m2+伊立替康180 mg/m2+5-FU推注400 mg/m2 d1+5-FU 2400 mg/m2 civ q2w.

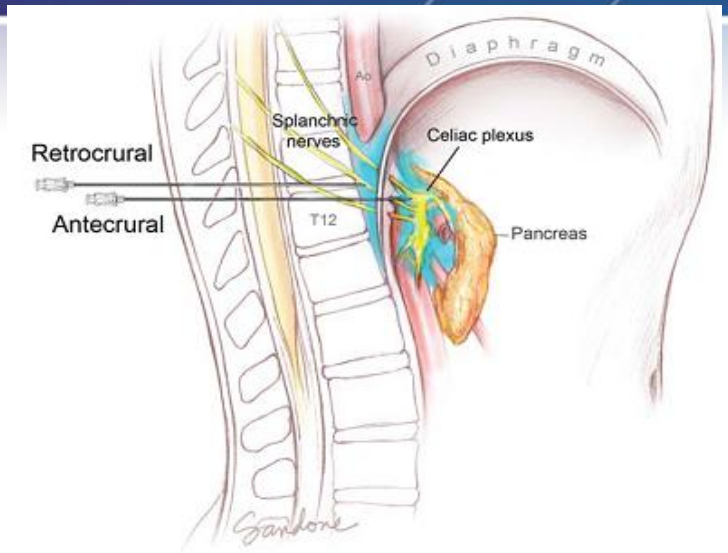
- 343例：中位生存6.8个月:11.1个月

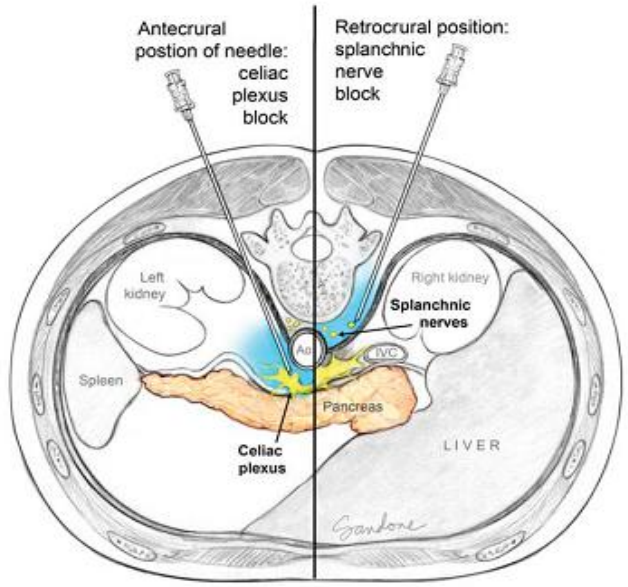
- 对于ES评分0-1者，为一线方案，但剂量需要减少或调整

Pain Assessment and Treatment

- 诊断时有65-75%病人有疼痛
- 需要吗啡或羟考酮止痛
- 顽固性疼痛需要行腹腔神经丛阻滞或毁损术，镇痛泵也用于顽固性疼痛
- 放疗用于姑息止痛有效，一般为原发肿瘤灶加部分正常组织边缘30-36Gy（2.4-3Gy/次）

Pain Assessment and Treatment





Patient is prone; viewed from feet looking towards head

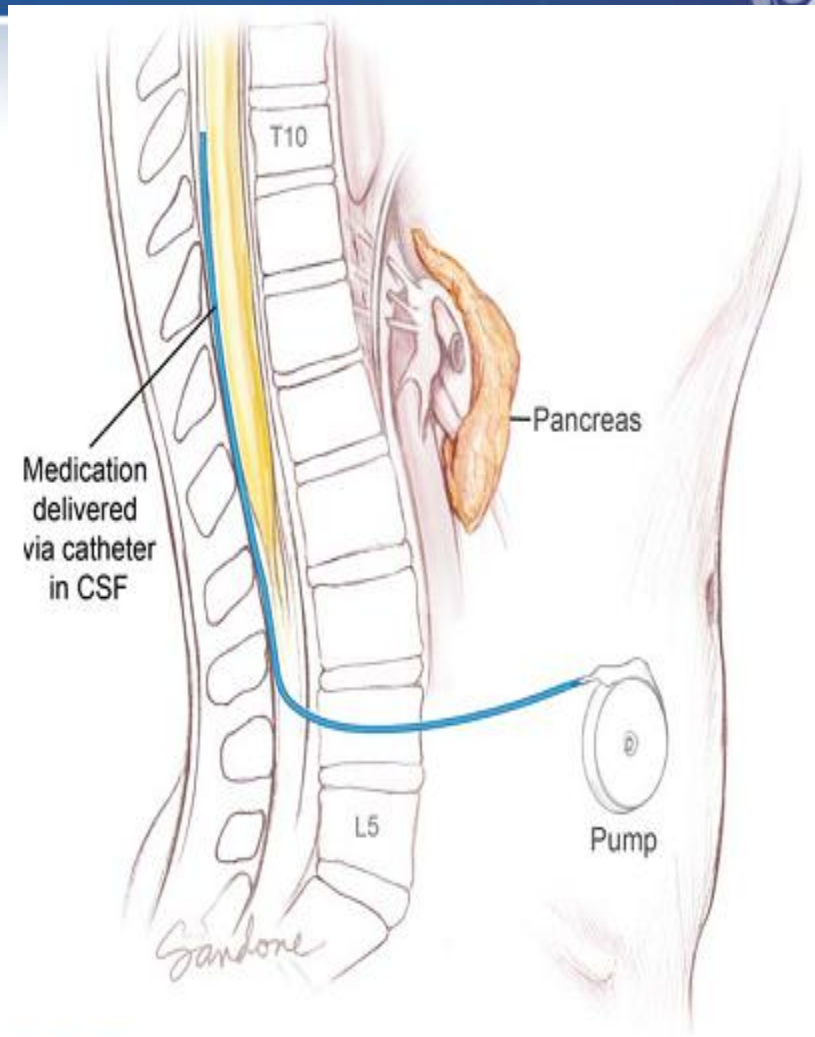


FIGURE 16. Pain Medication Can Also be Delivered Intrathecally into the Cerebrospinal Fluid (CSF) Using a Catheter Attached to a Surgically Implanted Pump. Blue represents the injected anesthetic. Illustration by Corinne Sandone. © Johns Hopkins University; used with permission.

总结

- 嗜烟、3年内新发糖尿、超过2年的慢性胰腺炎、家族有胰腺癌亲属、抑郁为胰腺癌高危因素
- SMAD4基因突变者有更高的转移和更差的预后
- SMV和门静脉能否重建、SMA和腹腔干的肿瘤接触面是否大于180度、腹主动脉有无受累是能否手术的关键
- 内镜下支架置入术能迅速解除黄疸或胃肠出口梗阻症状，减轻癌痛改善病人一般状态，对后续治疗很重要

总结

- 手术是唯一的治愈手段，R1切除与非手术治疗对比没有生存获益

- 能切除病人术后辅助化疗或化放疗有明显生存获益，建议化疗时间超过于6个月

- 可切除病人推荐先诱导化疗或化放疗，有15-35%病人因进展而避免了不必要的手术

- 不可切除病人推荐吉西他滨-base或5-Fu-base的诱导化疗后应该CT重新分期，除非**患者疼痛控制不佳或伴有局部梗阻症状。**S-1同期放化疗后S-1维持化疗中位生存达16.8个月，值得进一步研究

总结

- 转移性胰腺癌一线化疗推荐FOLFIRINOX方案，但需ES评分0-1分，且剂量需要调整

- 能手术：局部晚期：转移性　中位生存对比：

17-27个月：8-12个月：4-6个月,解除梗阻后的CA199水平有助于判断预后

- 放疗对局部控制及减轻局部疼痛、解除梗阻有益

术前放疗45-54Gy（1.8-2.5Gy/次）或36Gy/15次

术后辅助放疗45Gy，瘤床在R1切除推量5-15Gy

姑息放疗50.4-54Gy