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新辅助化疗在胰腺癌中的临床应用与进展

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摘　要

目前胰腺癌的根治性手段仍是手术切除，但大部分确诊患者并不适合手术治疗。多项大型多中心试验已初步证实新辅助化疗在胰腺癌中具有缩小肿瘤病灶、降低肿瘤分期、提高R0切除率，以及减少神经和淋巴管侵犯、减少微转移灶，进而降低患者的术后并发症、改善预后的作用。但在不同分期的胰腺癌化疗中，其有效性仍存在争议，需要更多的循证医学依据。至今，新辅助化疗并无标准方案，目前临床上大多采用FOLFIRINOX/改良FOLFIRINOX和AG方案，并已取得不错的疗效。此外，正在进行的相关试验也在进一步探索新型新辅助化疗方案。影像学和血清标志物可反映患者化疗的疗效，评价治疗缓解程度，但其准确性仍具有争议，需探索更多的可靠标准。

关键词

胰腺癌，新辅助化疗，方案选择，疗效评估

Clinical Application and Progress of Neoadjuvant Chemotherapy in Pancreatic Cancer

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Abstract

Currently, surgical resection remains the only curative treatment for pancreatic cancer; however,

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the majority of diagnosed patients are not candidates for surgery. Several large, multicenter trials have preliminarily confirmed that neoadjuvant chemotherapy can reduce tumor size, lower tumor staging, improve the R0 resection rate, and decrease nerve and lymphatic invasion, as well as minimize micro-metastases. This, in turn, can reduce postoperative complications and improve patient prognosis. However, the efficacy of chemotherapy at different stages of pancreatic cancer remains controversial, and more evidence from clinical trials is needed. To date, there is no standard neoadjuvant chemotherapy regimen, with most clinicians using FOLFIRINOX, modified FOLFIRINOX, or the AG regimen, all of which have shown promising results. Furthermore, ongoing trials are continuing to explore novel neoadjuvant chemotherapy options. Imaging techniques and serum biomarkers can reflect the effectiveness of chemotherapy and assess treatment response, but their accuracy remains debated, and more reliable standards need to be established.

Keywords

Pancreatic Cancer, Neoadjuvant Chemotherapy, Treatment Regimen Selection, Efficacy Evaluation

1. 引言

胰腺导管细胞癌(Pancreatic Ductal Adenocarcinoma, PDAC)简称胰腺癌，其恶性程度极高，发病率约3%，五年生存率仅有12%左右，病死率在所有癌症中排第三位，是消化道常见恶性肿瘤之一[1]。预计在2040 年前，胰腺癌将成为癌症相关死亡原因的第二位，将仅次于肺癌[2] [3]。目前最有效的治疗手段仍然是根治性手术切除[4]。因其早期诊断困难，症状隐匿，导致大多数患者确诊时已处于中晚期，高达80%~85%人群不适合手术切除[5]。根据影像学上肿瘤与邻近血管位置以及有无远处转移，指南将胰腺癌分为可切除胰腺癌(Resectable Pancreatic Cancer, RPC)、交界可切除胰腺癌(Borderline Resectable Pancreatic cancer, BRPC)、局部进展期胰腺癌(Locally Advanced Pancreatic Cancer, LAPC)和合并远处转移的胰腺癌四大类[6]。对于初诊 RPC 患者，建议行手术探查和根治性切除。尽管如此，也只有近 20%的患者可以获得R0 切除[7]。不幸的是，即使成功实现 R0 切除，一年内仍有高达 30%的患者出现远处复发[8]。

越来越多的研究表明，新辅助化疗可以缩小肿瘤病灶、降低分期、提高 R0 切除率、减少神经和淋巴管侵犯以及微转移灶，进而降低术后并发症、改善患者预后从而延长生存时间[7] [9] [10]。此外，一项大型多中心研究表明，胰腺癌患者进行新辅助化疗可显著改善肿瘤的病理反应、降低 CA 19-9 值以及提高患者的生存期[11]。近来，新辅助化疗已成为胰腺癌研究的重点话题。笔者就当前新辅助化疗在胰腺癌的最新应用与进展进行综述，希望对未来临床工作者在患者的药物方案选择时提供参考价值。

2. 胰腺癌新辅助化疗的研究现况

随着手术技术的不断提高，该病的切除率与安全性显著提高，患者围手术期并发症发生率有所改善。即使联合术后辅助治疗的应用，大多数病人的整体预后并未显著改善，在临床上胰腺癌的治疗仍极具挑战。胰腺癌的新辅助化疗最早由 Evans 教授在 1992 年提出[12]。近年来，随着大众对疾病认知和治疗模式的转变，新辅助化疗在胰腺癌中的应用价值逐渐成为学者探讨的重点。但关于化疗后最佳手术时机、术中淋巴结清扫范围、动脉切除重建范围、术后是否需要辅助治疗等问题仍缺乏共识[13]。新辅助化疗的拥护者认为，其可以提供更加有效的整体治疗，有效减少术后并发症，同时更容易地消除微转移灶。另

一方面，新辅助化疗的使用也带来了肿瘤局部进展、转移和化疗相关不良反应等风险，甚至使患者失去手术机会[14]。

目前国际上相关多中心大型研究已陆续开展。日本胰腺外科协会(Japanese Society of Pancreatic Surgery, JSPS)分析了 884 例胰腺癌患者的临床资料，结果表明，相比于先行手术的患者，接受了新辅助化疗的 211 例患者的总生存期(Overall Survival, OS)从 19.0 个月显著延长到 25.7 个月，并提高了 R0 切除率[15]。Versteijne 教授等人分析比较了先行手术与新辅助化疗在 RPC/BRPC 患者中的疗效。结果表明，接受新辅助化疗的中位 OS (18.8 个月)优于先行手术的 OS (14.8 个月) [16]。在另一项研究中也得到相似的结果[17]。在 Versteijne 教授随后发表的 PREOPANC 试验中，新辅助放化疗组中位 OS 为 15.7 个月，而先行手术组为 14.3 个月，两者具有显著差异($P = 0.025$)。此外，接受新辅助化疗的患者 5 年生存率为 20.5%，明显高于先行手术组的 6.5%，且 R0 切除率明显提高(72%与 43%，$p < 0.001$) [18]。

2.1. RPC 的新辅助化疗进展

最新美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)和美国临床肿瘤学会(American Society of Clinical Oncology, ASCO)均推荐 RPC 患者可直接行肿瘤切除手术治疗，再行 6 个月的术后辅助化疗。但对于有高危因素的人群，如血清 CA19-9 水平高、原发肿瘤较大、淋巴结广泛转移、严重消瘦和极度疼痛等，推荐行新辅助治疗[6] [19]。迄今为止，许多评价新辅助化疗方案的试验将 RPC 和 BRPC 的患者合并在一起，掩盖了 RPC 患者的真实治疗效果[16] [18] [20] [21]。因担心新辅助化疗延迟手术时间会提高疾病进展的风险，目前仅有少数专门针对 RPC 患者的临床试验开展。PACT-15 试验是意大利首个针对 RPC 的多中心、开放 II 期随机对照试验。研究中共纳入 88 例患者，结果显示相较于先行手术，新辅助 PEXG 方案化疗组(顺铂、表柔比星、吉西他滨和卡培他滨)成功将患者的中位 OS 延长至 38.2 个月，证明了在 RPC 患者进行新辅助化疗的可行性[22]。在日本进行的 Prep-02/JSAP-05 研究中，接受新辅助化疗的 RPC 患者的中位 OS 显著提高；然而，手术切除率、R0 切除率、术后并发症发生率和死亡率却并无显著差异[23]。在近期结束的 NEONAX (AIO-PAK-0313)试验结果中，与先行手术组相比，新辅助组 R0 切除率更高(88%与 67%)，中位 OS 为 25.5 个月，显著高于先行手术组的 16.7 个月；中位无病生存期(Disease-Free Survival, DFS)也更长[24]。但是，RPC 患者进行新辅助化疗依旧存在着争议。质疑者认为这存在着使疾病进展成不可切除状态的风险。据报道，这种风险率高达 16% [25]。此外，新辅助化疗与先行手术组相比 1 年 OS 并没有显著增加[26]。国际 II 期试验 NORPACT-1 也并未证明与前期手术相比，四药联合的新辅助 FOLFIRINOX 方案(奥沙利铂、伊立替康、5-氟尿嘧啶和亚叶酸钙)具有生存获益[27]。因此，对于 RPC 患者，新辅助化疗的选择及是否有其优越性、是否有益于后续治疗，仍存在困惑。正在进行的相关临床试验有望为 RPC 患者群体建立最合适的新辅助化疗方案[28] [29]。

2.2. BRPC 的新辅助化疗进展

有研究证明，新辅助化疗在 BRPC 中发挥着重要作用。它不仅可以缩小肿瘤，使肿瘤更易于被切除，提高 R0 切除率，还可以最大限度地降低早期无法被检测到的微小转移病灶和淋巴结受累的发生率，从而改善患者整体预后[30] [31]。相关指南均推荐 BRPC 患者优先考虑新辅助化疗[6] [19]。Versteijne 教授在 PREOPANC-1 试验中纳入了 113 例 BRPC 患者(新辅助组 54 例，先行手术组 59 例)，经化疗后两组中位 OS 分别为 17.6 个月和 13.2 个月，中位 DFS 分别为 6.3 个月和 6.2 个月，R0 切除率分别为 79%和 13%[21]。这提示新辅助放化疗组具有更高的 DFS、更少的病理淋巴结数、更低的周围神经浸润和静脉浸润的发生率。同时，生存分析发现术前新辅助化疗的生存率明显提高(35.2 个月与 19.8 个月，$p = 0.029$)。然而，在 BRPC 组患者中，新辅助组和先行手术组发生严重不良事件的患者比例分别为 50%和 36% ($p = 0.130$)，

这提示我们在选择药物时需进一步评估患者病情和治疗获益[21]。在随访时间更长的分析中，新辅助化疗组的 DFS、中位 OS、3 年和 5 年生存率均得到显著提高[18]。多中心 ESPAC-5 筛选了 86 例 BRPC 患者，随机分配到先行手术组、吉西他滨加卡培他滨组、FOLFIRINOX 组和基于卡培他滨的放化疗组。发现先行手术组的手术切除率为 68%，合并新辅助治疗组为 55%；先行手术组中 14%的患者进行了 R0 切除，而联合新辅助治疗组有 23%。该试验中新辅助化疗虽未明显提高 BRPC 患者的(R0)切除率，但却显著改善了患者的生存率(先行手术组的 1 年 OS 为 39%，新辅助治疗组为 76%，$p = 0.0052$)。其中 FOLFIRINOX 方案以及吉西他滨联合卡培他滨的新辅助化疗方案与先行手术组相比，一年生存率、DFS 均明显提高[32]。然而，Eshmuminov 教授近期的研究发现，在成功实施肿瘤切除术的 BRPC 患者中，新辅助 FOLFIRINOX 化疗的 OS (32.9 个月)与吉西他滨联合白蛋白结合型紫杉醇(AG)化疗(28.6 个月，$p = 0.285$)、吉西他滨联合其他药物化疗(38.8 个月，$p = 0.1$)、吉西他滨单药化疗(23.1 个月，$p = 0.083$)相比，并没有明显差异[33]。提示我们在临床选择新辅助化疗方案时，需进行严谨的抉择，以为患者提供最佳治疗。

2.3. LAPC 的新辅助化疗进展

在初诊患者中，LAPC 占比较大。其既往被归为不可切除胰腺癌的范畴，根据 NCCN 指南定义，这类患者虽没有远处转移的证据，但局部区域的血管侵犯明显。因此治疗策略多以转化诱导(化疗联合或不联合放疗)为主，已达到降期的目的[6]。国际多中心 II 期 LAPACT 试验发现在行 6 个周期 AG 方案后，有 16%的患者获得手术切除机会(7 名 R0 切除，9 名 R1 切除)，患者中位无进展生存期(Progression-Free Survival, PFS)达到 10.9 个月，中位 OS 达到 18.8 个月，优于未行切除术的患者。化疗期间的疾病控制率(Disease Control Rate, DCR)为 77.6%，客观反应率(Objective Response Rate, ORR)为 33.6%。此外，未发生治疗相关不良事件导致的死亡，且大多数患者生活质量较好[34]。NEOLAP-AIO-PAK-0113 试验中选取了 130 名接受 AG 方案化疗的 LAPC 患者，研究者将他们随机分配到 AG 组(64 例)或 FOLFIRINOX 组(66 例)。AG 组切除率为 35.9%，FOLFIRINOX 组为 43.9%。AG 组的中位 OS 为 18.5 个月，FOLFIRINOX 组为 20.7 个月，$p = 0.53$。两组在诱导化疗期间出现 3~4 级不良事件的发生率相近。结果表明 FOLFIRINOX 作为 LAPC 的诱导化疗方案具有与 AG 相似的活性和安全性[35]。Marthey 等人的研究也发现 FOLFIRINOX 在治疗 LAPC 患者有效且毒性可控[36]。

3. 胰腺癌的新辅助化疗方案

关于胰腺癌的新辅助化疗方案，目前国际上并未有统一标准，加之各中心的方案差异较大，所以，相关具体化疗方案并未达到共识。新辅助化疗的主要目的是控制肿瘤进展、降低肿瘤负荷，甚至提高 R0 切除率等。为提高疗效，最新指南建议采用多药联合的治疗方案，如 FOLFIRINOX/改良 FOLFIRINOX 和 AG 方案[37]。

FOLFIRINOX 是目前常用的一线治疗方案，在广泛临床应用的过程中已证实其效果远优于吉西他滨单药治疗。2011 年，Conroy 等人首次发表了关于 FOLFIRINOX 方案在晚期胰腺癌的研究，发现该方案可有高达 31.6%的 ORR，远高于吉西他滨单药的疗效(9.4%, $p < 0.001$)。此外，其中位 OS、PFS 均明显延长[38]。但 3 或 4 级中性粒细胞减少、发热性中性粒细胞减少、血小板减少、腹泻和感觉神经病变的发生率在 FOLFIRINOX 方案组的大胜率明显较高，而 3 或 4 级丙氨酸氨基转移酶水平升高的发生率在吉西他滨组明显较高[38]。一项回顾性研究分析了 11 项临床研究中 315 例接受 FOLFIRINOX 方案作为一线治疗的初治 LAPC 患者，发现约 1/4 的患者在化疗后成功实现肿瘤切除，R0 切除率高达 75%，中位 OS 和 PFS 分别为 24.2 个月和 15.0 个月[39]。此外，Choi 等人发现，在 BRPC/LAPC 患者的新辅助化疗中，与先行手术后辅助吉西他滨或吉西他滨联合卡培他滨化疗相比，新辅助 FOLFIRINOX 化疗的中位 OS 和中

位 DFS 更好[40]。且从成本效益的角度来看，新辅助 FOLFIRINOX 的成本效果比(46,200 美元)优于吉西他滨联合卡培他滨(83,600 美元)。

然而，FOLFIRINOX 作为四药联用方案，在疗效显著的同时难免副作用亦明显，主要表现在血液系统和消化系统毒性[41]，如贫血、白细胞减少、血小板降低恶心、呕吐、腹泻等，导致部分患者不能耐受，从而难以继续化疗。因此，研究者们对该方案进行了不同方式的改良，以求在不影响疗效的同时减少药物不良反应[42]-[45]。Memorial Sloan Kettering 癌症中心的研究报告显示，在转移性或局部晚期患者中 FOLFIRINOX 方案可以 80%的剂量浓度表现出良好的活性和可接受的毒性[42]。在转移性胰腺癌中，Stein 等人将方案中 5-FU 和伊立替康的初始剂量分别减少了 25%后，改良 FOLFIRINOX 的疗效与 FOLFIRINOX 相当。此外，在 LAPC 中疗效显著，ORR 为 17.2%，切除率为 41.9%，中位 OS 和 PFS 分别为 26.6 个月和 17.8 个月。可喜的是，接受改良方案的患者中性粒细胞减少、疲劳和呕吐的发生率显著降低[43]。类似的，有研究报导改良 FOLFIRINOX 与标准剂量 FOLFIRINOX 在 OS、PFS、ORR、DCR 均无明显差异，但前者具有更好的安全性[44]。在国内 LAPC 人群中开展的研究也发现，改良 FOLFIRINOX 方案可显著降低 CA19-9 水平和肿瘤直径，且相较于先行手术治疗，具有更高的生存获益[45]。改良 FOLFIRINOX 方案在体力状况良好(美国东部肿瘤协作组 ECOG 评分 0~1 分)的患者中可达到满意的效果[46]。

胰腺癌的肿瘤间质丰富，而肿瘤间质屏障的存在会使化疗药物难以到达肿瘤局部而起效[47]。研究发现，AG 方案给药可耗竭肿瘤间质、增加局部药物浓度、消退肿瘤等[48]。Von Hoff 等人在大型 III 期试验中发现，与吉西他滨单药治疗的中位 OS 相比，AG 方案治疗将其从 6.7 个月提高到了 8.5 个月[49]。由于其较 FOLFIRINOX 具有良好的耐受性，此后该方案在临床中迅速被采用。在 LAPACT 研究中，行 AG 方案的 LAPC 患者，切除率达 16%。且相较于未手术的患者，中位 PFS 和 OS 更长。治疗期间的 DCR 为 77.6%，ORR 为 33.6%，患者生活质量得到明显提升[34]。同样的，多中心 GISCAD II 期试验结果表明，相较于吉西他滨治疗，接受 AG 治疗的 LAPC 患者疾病进展率明显更低。虽然中位 OS 相近，但反应率和中位 PFS 均高于吉西他滨组[50]。此外，Miyasaka 等在 BRPC 患者中对比了新辅助 AG 方案和先行手术的疗效，发现 AG 方案组的手术时间更短、失血量更少、R0 切除率更高，并且 DFS 和 OS 较先行手术组均显著延长[51]。

其他方案如吉西他滨单药、吉西他滨联合替吉奥、卡培他滨等，亦有一定的疗效，但主要用于体力状况较差者、无手术希望并且无法耐受一线化疗方案的患者，以达到改善患者生活质量、延长生存时间的目的[32] [52] [53]。近期，新型伊立替康脂质体因其结构更稳定、抑癌作用更强、安全性更高的优势，在今年发表的 PAN-HEROIC-1 研究中与氟尿嘧啶(5-FU)和亚叶酸钙(LV)联合应用，被证明在既往经吉西他滨为基础的化疗方案治疗失败的 LAPC 和转移性胰腺癌患者中显示出肯定的疗效和安全性[54]。当然，在大量更高等级的循证依据出现之前，具体哪种方式最适合作为胰腺癌的新辅助化疗标准方案仍为时尚早。已结束和目前进行的研究中相关治疗方案较多[23] [55] [56]，各有其优缺点，但仍需要继续进行大规模的研究来验证。

4. 疗效评估依据

目前化疗疗效评估手段主要依赖于影像学检查和血清标志物指标变化(如 CA19-9、CA12-5、CEA、miRNA 等)，评估手段相对不足。CA19-9 是目前应用最广泛、最重要的胰腺癌生物标志物[57]。但其易受多种因素干扰，如炎症感染等。单纯一种指标升高或降低来评价新辅助疗效的特异度不高。此外，人群中存在大约 5%~10% Lewis 抗原阴性的患者，他们很少或没有 CA19-9 分泌，导致其诊断的特异度降低[58]。尽管有研究表明，CEA 和 CA125 比其他生物标志物更敏感，但尚未展现足够的临床应用价值[59]。此外，miRNA 作为生物标志物在各种癌症实体中具有诊断、预后和预测作用，并且通过 miRNA 的表达特征，还可以明确地区分健康、炎症和癌变的胰腺组织[60] [61]。

影像学可以确定新辅助化疗后的代谢和生物学反应[62]。增强 CT 扫描(Contrast-Enhanced Computed Tomography)是胰腺癌常规的、代表性的影像学首诊方法，其优点包括较高的空间分辨率和多平面重建能力[63]。但患者经过新辅助化疗后 CT 便不再是可靠的评估手段，这可能与治疗后肿瘤大小、与血管接触关系、纤维化形成等有关，并可能会高估肿瘤的不可切除性[64]。尽管存在局限性，但有学者发现 CT 图像上肿瘤密度的变化仍可能有助于预测 R0 切除以及肿瘤的均匀性[65]。然而，为进一步确定肿瘤组织学反应，仍需积极对病情稳定或有缓解的患者实行手术探查[65]。此外，有学者对比了 MRI 和 CT 在新辅助化疗前后评估肿瘤大小方面的差异，发现 MRI 和 CT 之间的肿瘤大小一致性极好，两种测量方式具有相似的性能($p = 1.0$) [66]。同时，在对新辅助化疗后成功行切除肿瘤患者的研究中，研究者发现 FDG-PET 能高度预测病理反应和生存率[67]。并推荐使用 FDG-PET/CT 或 PET/MRI 用于预测和评估 RPC 或 BRPC 患者对新辅助化疗的反应[68]。

传统的基于影像学解剖肿瘤大小的反应评估系统，如世界卫生组织(WHO)标准和实体瘤反应评估标准(Response Evaluation Criteria in Solid Tumors, RECIST)1.0 和 1.1，目前已广泛用于临床试验，以确定全身治疗对各种恶性肿瘤的疗效[68]-[71]。尽管形态学评估在评估转移性疾病方面取得了成功，但对于治疗后局部反应、肿瘤体积改变不明显的患者，其早期评价的意义有限。此外，胰腺癌大多为浸润性，边界不清且形状不规则，且由于邻近受累血管的复杂性，精确评估肿瘤大小是具有挑战性的[72]。因此，构建可以准确评价治疗缓解程度的可靠标准至关重要。病理学评估同样具有重要的价值意义。目前临床上多应用 Evans 系统、CAP 系统、Chatterjee 系统和 Hartman 系统来进行新辅助治疗后的肿瘤评估。然而，哪种系统更适用于胰腺癌治疗的疗效评估尚无共识。Lee 等人分别将四种评估系统用于新辅助化疗后的胰腺癌患者，结果表明每种系统评价结果与患者的预后均无显著相关性[73]。可喜的是，经新辅助化疗后患者，病理学评估为完全病理反应的患者有更高的生存率[74]。此外，经治疗后患者机体组成的变化也可能用于评估新辅助的疗效。研究表明，患者在新辅助期间肌肉组织的增加与可切除性相关；同时，脂肪含量越大，肿瘤无法切除的风险也越大[75]。

5. 小结

近年来，新辅助化疗在胰腺癌领域迅速发展，国内外已陆续开展相关临床试验，并得到了可喜的结果。虽然有可能导致患者失去手术机会的风险，但越来越多的研究证据表明其具有提高 R0 切除率、延长生存期、改善预后等方面的益处，且国内外发表的相关指南和共识也对其进行了规范化制定和应用推荐。然而，目前关于化疗方案的标准化制定、疗效评估方法的进一步补充等问题亟待解决，后续仍需要更多高质量的大型多中心临床试验来进一步验证。相信随着循证依据的进一步补充，同时结合放疗、分子靶向治疗、免疫治疗等综合治疗手段，胰腺癌患者的预后和生存率会得到明显提高。

参考文献

[1] Siegel, R.L., Miller, K.D., Fuchs, H.E. and Jemal, A. (2022) Cancer Statistics, 2022. *CA*: *A Cancer Journal for Clinicians*, **72**, 7-33. https://doi.org/10.3322/caac.21708

[2] Rahib, L., Wehner, M.R., Matrisian, L.M. and Nead, K.T. (2021) Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Network Open*, **4**, e214708. https://doi.org/10.1001/jamanetworkopen.2021.4708

[3] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[4] Blair, A.B., Rosati, L.M., Rezaee, N., Gemenetzis, G., Zheng, L., Hruban, R.H., *et al.* (2018) Postoperative Complications after Resection of Borderline Resectable and Locally Advanced Pancreatic Cancer: The Impact of Neoadjuvant Chemotherapy with Conventional Radiation or Stereotactic Body Radiation Therapy. *Surgery*, **163**, 1090-1096. https://doi.org/10.1016/j.surg.2017.11.027

[5] Rawla, P., Sunkara, T. and Gaduputi, V. (2019) Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. *World Journal of Oncology*, **10**, 10-27. https://doi.org/10.14740/wjon1166

[6] Tempero, M.A., Malafa, M.P., Al-Hawary, M., Behrman, S.W., Benson, A.B., Cardin, D.B., *et al.* (2021) Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, **19**, 439-457. https://doi.org/10.6004/jnccn.2021.0017

[7] Schorn, S., Demir, I.E., Reyes, C.M., Saricaoglu, C., Samm, N., Schirren, R., *et al.* (2017) The Impact of Neoadjuvant Therapy on the Histopathological Features of Pancreatic Ductal Adenocarcinoma—A Systematic Review and Meta-Analysis. *Cancer Treatment Reviews*, **55**, 96-106. https://doi.org/10.1016/j.ctrv.2017.03.003

[8] Tummers, W.S., Groen, J.V., Sibinga Mulder, B.G., Farina-Sarasqueta, A., Morreau, J., Putter, H., *et al.* (2019) Impact of Resection Margin Status on Recurrence and Survival in Pancreatic Cancer Surgery. *British Journal of Surgery*, **106**, 1055-1065. https://doi.org/10.1002/bjs.11115

[9] Halbrook, C.J., Lyssiotis, C.A., Pasca di Magliano, M. and Maitra, A. (2023) Pancreatic Cancer: Advances and Challenges. *Cell*, **186**, 1729-1754. https://doi.org/10.1016/j.cell.2023.02.014

[10] Cloyd, J.M., Wang, H., Egger, M.E., Tzeng, C.D., Prakash, L.R., Maitra, A., *et al.* (2017) Association of Clinical Factors with a Major Pathologic Response Following Preoperative Therapy for Pancreatic Ductal Adenocarcinoma. *JAMA Surgery*, **152**, 1048-1056. https://doi.org/10.1001/jamasurg.2017.2227

[11] Macedo, F.I., Ryon, E., Maithel, S.K., Lee, R.M., Kooby, D.A., Fields, R.C., *et al.* (2019) Survival Outcomes Associated with Clinical and Pathological Response Following Neoadjuvant FOLFIRINOX or Gemcitabine/Nab-Paclitaxel Chemotherapy in Resected Pancreatic Cancer. *Annals of Surgery*, **270**, 400-413. https://doi.org/10.1097/sla.0000000000003468

[12] Evans, D.B. (1992) Preoperative Chemoradiation and Pancreaticoduodenectomy for Adenocarcinoma of the Pancreas. *Archives of Surgery*, **127**, 1335-1339. https://doi.org/10.1001/archsurg.1992.01420110083017

[13] Wu, H., Li, J., Li, J., Zhai, Q., Ye, J., Zheng, S., *et al.* (2023) Comprehensive Multimodal Management of Borderline Resectable Pancreatic Cancer: Current Status and Progress. *World Journal of Gastrointestinal Surgery*, **15**, 142-162. https://doi.org/10.4240/wjgs.v15.i2.142

[14] Springfeld, C., Ferrone, C.R., Katz, M.H.G., Philip, P.A., Hong, T.S., Hackert, T., *et al.* (2023) Neoadjuvant Therapy for Pancreatic Cancer. *Nature Reviews Clinical Oncology*, **20**, 318-337. https://doi.org/10.1038/s41571-023-00746-1

[15] Nagakawa, Y., Sahara, Y., Hosokawa, Y., Murakami, Y., Yamaue, H., Satoi, S., *et al.* (2019) Clinical Impact of Neoadjuvant Chemotherapy and Chemoradiotherapy in Borderline Resectable Pancreatic Cancer: Analysis of 884 Patients at Facilities Specializing in Pancreatic Surgery. *Annals of Surgical Oncology*, **26**, 1629-1636. https://doi.org/10.1245/s10434-018-07131-8

[16] Versteijne, E., Vogel, J.A., Besselink, M.G., Busch, O.R.C., Wilmink, J.W., Daams, J.G., *et al.* (2018) Meta-Analysis Comparing Upfront Surgery with Neoadjuvant Treatment in Patients with Resectable or Borderline Resectable Pancreatic Cancer. *British Journal of Surgery*, **105**, 946-958. https://doi.org/10.1002/bjs.10870

[17] Inoue, Y., Saiura, A., Oba, A., Ono, Y., Mise, Y., Ito, H., *et al.* (2020) Neoadjuvant Gemcitabine and Nab-Paclitaxel for Borderline Resectable Pancreatic Cancers: Intention-to-Treat Analysis Compared with Upfront Surgery. *Journal of Hepato-Biliary-Pancreatic Sciences*, **28**, 143-155. https://doi.org/10.1002/jhbp.844

[18] Versteijne, E., van Dam, J.L., Suker, M., Janssen, Q.P., Groothuis, K., Akkermans-Vogelaar, J.M., *et al.* (2022) Neoadjuvant Chemoradiotherapy versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial. *Journal of Clinical Oncology*, **40**, 1220-1230. https://doi.org/10.1200/jco.21.02233

[19] Khorana, A.A., McKernin, S.E., Berlin, J., Hong, T.S., Maitra, A., Moravek, C., *et al.* (2019) Potentially Curable Pancreatic Adenocarcinoma: ASCO Clinical Practice Guideline Update. *Journal of Clinical Oncology*, **37**, 2082-2088. https://doi.org/10.1200/jco.19.00946

[20] van Dam, J.L., Janssen, Q.P., Besselink, M.G., Homs, M.Y.V., van Santvoort, H.C., van Tienhoven, G., *et al.* (2022) Neoadjuvant Therapy or Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: A Meta-Analysis of Randomised Controlled Trials. *European Journal of Cancer*, **160**, 140-149. https://doi.org/10.1016/j.ejca.2021.10.023

[21] Versteijne, E., Suker, M., Groothuis, K., Akkermans-Vogelaar, J.M., Besselink, M.G., Bonsing, B.A., *et al.* (2020) Preoperative Chemoradiotherapy versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *Journal of Clinical Oncology*, **38**, 1763-1773. https://doi.org/10.1200/jco.19.02274

[22] Reni, M., Balzano, G., Zanon, S., Zerbi, A., Rimassa, L., Castoldi, R., *et al.* (2018) Safety and Efficacy of Preoperative or Postoperative Chemotherapy for Resectable Pancreatic Adenocarcinoma (PACT-15): A Randomised, Open-Label, Phase 2-3 Trial. *The Lancet Gastroenterology & Hepatology*, **3**, 413-423. https://doi.org/10.1016/s2468-1253(18)30081-5

[23] Motoi, F., Kosuge, T., Ueno, H., Yamaue, H., Satoi, S., Sho, M., *et al.* (2019) Randomized Phase II/III Trial of Neoadjuvant Chemotherapy with Gemcitabine and S-1 versus Upfront Surgery for Resectable Pancreatic Cancer (Prep-02/JSAP05). *Japanese Journal of Clinical Oncology*, **49**, 190-194. https://doi.org/10.1093/jjco/hyy190

[24] Seufferlein, T., Uhl, W., Kornmann, M., Algül, H., Friess, H., König, A., *et al.* (2023) Perioperative or Only Adjuvant Gemcitabine Plus Nab-Paclitaxel for Resectable Pancreatic Cancer (NEONAX)—A Randomized Phase II Trial of the AIO Pancreatic Cancer Group. *Annals of Oncology*, **34**, 91-100. https://doi.org/10.1016/j.annonc.2022.09.161

[25] Zhan, H., Xu, J., Wu, D., Wu, Z., Wang, L., Hu, S., *et al.* (2017) Neoadjuvant Therapy in Pancreatic Cancer: A Systematic Review and Meta-Analysis of Prospective Studies. *Cancer Medicine*, **6**, 1201-1219. https://doi.org/10.1002/cam4.1071

[26] Schwarz, L., Vernerey, D., Bachet, J., Tuech, J., Portales, F., Michel, P., *et al.* (2018) Resectable Pancreatic Adenocarcinoma Neo-Adjuvant FOLF(IRIN)OX-Based Chemotherapy—A Multicenter, Non-Comparative, Randomized, Phase II Trial (PANACHE01-PRODIGE48 Study). *BMC Cancer*, **18**, Article No. 762. https://doi.org/10.1186/s12885-018-4663-4

[27] Labori, K.J., Bratlie, S.O., Andersson, B., Angelsen, J., Biörserud, C., Björnsson, B., *et al.* (2024) Neoadjuvant FOLFIRINOX versus Upfront Surgery for Resectable Pancreatic Head Cancer (NORPACT-1): A Multicentre, Randomised, Phase 2 Trial. *The Lancet Gastroenterology & Hepatology*, **9**, 205-217. https://doi.org/10.1016/s2468-1253(23)00405-3

[28] Eade, A.V., Friedman, L.R., Larrain, C., Rainey, A., Hernandez, J.M., Chawla, A., *et al.* (2024) ALLIANCE A021806: A Phase III Trial of Perioperative versus Adjuvant Chemotherapy for Resectable Pancreatic Cancer. *Annals of Surgical Oncology*, **31**, 6373-6374. https://doi.org/10.1245/s10434-024-15817-5

[29] Janssen, Q.P., van Dam, J.L., Bonsing, B.A., Bos, H., Bosscha, K.P., Coene, P.P.L.O., *et al.* (2021) Total Neoadjuvant FOLFIRINOX versus Neoadjuvant Gemcitabine-Based Chemoradiotherapy and Adjuvant Gemcitabine for Resectable and Borderline Resectable Pancreatic Cancer (PREOPANC-2 Trial): Study Protocol for a Nationwide Multicenter Randomized Controlled Trial. *BMC Cancer*, **21**, Article No. 300. https://doi.org/10.1186/s12885-021-08031-z

[30] Oba, A., Ho, F., Bao, Q.R., Al-Musawi, M.H., Schulick, R.D. and Del Chiaro, M. (2020) Neoadjuvant Treatment in Pancreatic Cancer. *Frontiers in Oncology*, **10**, Article 245. https://doi.org/10.3389/fonc.2020.00245

[31] Shaib, W.L., Ip, A., Cardona, K., Alese, O.B., Maithel, S.K., Kooby, D., *et al.* (2016) Contemporary Management of Borderline Resectable and Locally Advanced Unresectable Pancreatic Cancer. *The Oncologist*, **21**, 178-187. https://doi.org/10.1634/theoncologist.2015-0316

[32] Ghaneh, P., Palmer, D., Cicconi, S., Jackson, R., Halloran, C.M., Rawcliffe, C., *et al.* (2023) Immediate Surgery Compared with Short-Course Neoadjuvant Gemcitabine Plus Capecitabine, FOLFIRINOX, or Chemoradiotherapy in Patients with Borderline Resectable Pancreatic Cancer (ESPAC5): A Four-Arm, Multicentre, Randomised, Phase 2 Trial. *The Lancet Gastroenterology & Hepatology*, **8**, 157-168. https://doi.org/10.1016/s2468-1253(22)00348-x

[33] Eshmuminov, D., Aminjonov, B., Palm, R.F., Malleo, G., Schmocker, R.K., Abdallah, R., *et al.* (2023) FOLFIRINOX or Gemcitabine-Based Chemotherapy for Borderline Resectable and Locally Advanced Pancreatic Cancer: A Multi-Institutional, Patient-Level, Meta-Analysis and Systematic Review. *Annals of Surgical Oncology*, **30**, 4417-4428. https://doi.org/10.1245/s10434-023-13353-2

[34] Philip, P.A., Lacy, J., Portales, F., Sobrero, A., Pazo-Cid, R., Manzano Mozo, J.L., *et al.* (2020) Nab-Paclitaxel Plus Gemcitabine in Patients with Locally Advanced Pancreatic Cancer (LAPACT): A Multicentre, Open-Label Phase 2 Study. *The Lancet Gastroenterology & Hepatology*, **5**, 285-294. https://doi.org/10.1016/s2468-1253(19)30327-9

[35] Kunzmann, V., Siveke, J.T., Algül, H., Goekkurt, E., Siegler, G., Martens, U., *et al.* (2021) Nab-Paclitaxel Plus Gemcitabine versus Nab-Paclitaxel Plus Gemcitabine Followed by FOLFIRINOX Induction Chemotherapy in Locally Advanced Pancreatic Cancer (NEOLAP-AIO-PAK-0113): A Multicentre, Randomised, Phase 2 Trial. *The Lancet Gastroenterology & Hepatology*, **6**, 128-138. https://doi.org/10.1016/s2468-1253(20)30330-7

[36] Marthey, L., Sa-Cunha, A., Blanc, J.F., Gauthier, M., Cueff, A., Francois, E., *et al.* (2014) FOLFIRINOX for Locally Advanced Pancreatic Adenocarcinoma: Results of an AGEO Multicenter Prospective Observational Cohort. *Annals of Surgical Oncology*, **22**, 295-301. https://doi.org/10.1245/s10434-014-3898-9

[37] Tempero, M.A., Malafa, M.P., Chiorean, E.G., Czito, B., Scaife, C., Narang, A.K., *et al.* (2019) Guidelines Insights: Pancreatic Adenocarcinoma, Version 1.2019. *Journal of the National Comprehensive Cancer Network*, **17**, 202-210. https://doi.org/10.6004/jnccn.2019.0014

[38] Conroy, T., Desseigne, F., Ychou, M., Bouché, O., Guimbaud, R., Bécouarn, Y., *et al.* (2011) FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *New England Journal of Medicine*, **364**, 1817-1825. https://doi.org/10.1056/nejmoa1011923

[39] Suker, M., Beumer, B.R., Sadot, E., Marthey, L., Faris, J.E., Mellon, E.A., *et al.* (2016) FOLFIRINOX for Locally Advanced Pancreatic Cancer: A Systematic Review and Patient-Level Meta-analysis. *The Lancet Oncology*, **17**, 801-810. https://doi.org/10.1016/s1470-2045(16)00172-8

[40] Choi, J.G., Nipp, R.D., Tramontano, A., Ali, A., Zhan, T., Pandharipande, P., *et al.* (2018) Neoadjuvant FOLFIRINOX for Patients with Borderline Resectable or Locally Advanced Pancreatic Cancer: Results of a Decision Analysis. *The Oncologist*, **24**, 945-954. https://doi.org/10.1634/theoncologist.2018-0114

[41] Chung, M.J., Kang, H., Kim, H.G., Hyun, J.J., Lee, J.K., Lee, K.H., *et al.* (2018) Multicenter Phase II Trial of Modified FOLFIRINOX in Gemcitabine-Refractory Pancreatic Cancer. *World Journal of Gastrointestinal Oncology*, **10**, 505-515. https://doi.org/10.4251/wjgo.v10.i12.505

[42] Lowery, M.A., Yu, K.H., Adel, N.G., Apollo, A.J., Boyar, M.S., Caron, P., *et al.* (2012) Activity of Front-Line FOLFIRINOX (FFX) in Stage III/IV Pancreatic Adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC). *Journal of Clinical Oncology*, **30**, 4057-4057. https://doi.org/10.1200/jco.2012.30.15_suppl.4057

[43] Stein, S.M., James, E.S., Deng, Y., Cong, X., Kortmansky, J.S., Li, J., *et al.* (2016) Final Analysis of a Phase II Study of Modified FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer. *British Journal of Cancer*, **114**, 737-743. https://doi.org/10.1038/bjc.2016.45

[44] Kang, H., Jo, J.H., Lee, H.S., Chung, M.J., Bang, S., Park, S.W., *et al.* (2018) Comparison of Efficacy and Safety between Standard-Dose and Modified-Dose FOLFIRINOX as a First-Line Treatment of Pancreatic Cancer. *World Journal of Gastrointestinal Oncology*, **10**, 421-430. https://doi.org/10.4251/wjgo.v10.i11.421

[45] Li, X., Guo, C., Li, Q., Wei, S., Zhang, Q., Chen, Y., *et al.* (2018) Association of Modified-FOLFIRINOX-Regimen-Based Neoadjuvant Therapy with Outcomes of Locally Advanced Pancreatic Cancer in Chinese Population. *The Oncologist*, **24**, 301-e93. https://doi.org/10.1634/theoncologist.2018-0696

[46] He, M., Sun, J., Zhao, D., He, H., Wang, B., Xu, L., *et al.* (2019) Modified-FOLFIRINOX Combined with Deep Regional Hyperthermia in Pancreatic Cancer: A Retrospective Study in Chinese Patients. *International Journal of Hyperthermia*, **36**, 393-401. https://doi.org/10.1080/02656736.2019.1579371

[47] Miyashita, T., Tajima, H., Makino, I., *et al.* (2018) Neoadjuvant Chemotherapy with Gemcitabine Plus Nab-Paclitaxel Reduces the Number of Cancer-associated Fibroblasts through Depletion of Pancreatic Stroma. *Anticancer Research*, **38**, 337-343.

[48] Heinemann, V., Reni, M., Ychou, M., Richel, D.J., Macarulla, T. and Ducreux, M. (2014) Tumour-Stroma Interactions in Pancreatic Ductal Adenocarcinoma: Rationale and Current Evidence for New Therapeutic Strategies. *Cancer Treatment Reviews*, **40**, 118-128. https://doi.org/10.1016/j.ctrv.2013.04.004

[49] Von Hoff, D.D., Ervin, T., Arena, F.P., Chiorean, E.G., Infante, J., Moore, M., *et al.* (2013) Increased Survival in Pancreatic Cancer with Nab-Paclitaxel Plus Gemcitabine. *New England Journal of Medicine*, **369**, 1691-1703. https://doi.org/10.1056/nejmoa1304369

[50] Cascinu, S., Berardi, R., Bianco, R., Bilancia, D., Zaniboni, A., Ferrari, D., *et al.* (2021) Nab-Paclitaxel/Gemcitabine Combination Is More Effective than Gemcitabine Alone in Locally Advanced, Unresectable Pancreatic Cancer—A GISCAD Phase II Randomized Trial. *European Journal of Cancer*, **148**, 422-429. https://doi.org/10.1016/j.ejca.2021.02.023

[51] Miyasaka, Y., Ohtsuka, T., Kimura, R., Matsuda, R., Mori, Y., Nakata, K., *et al.* (2019) Neoadjuvant Chemotherapy with Gemcitabine Plus Nab-Paclitaxel for Borderline Resectable Pancreatic Cancer Potentially Improves Survival and Facilitates Surgery. *Annals of Surgical Oncology*, **26**, 1528-1534. https://doi.org/10.1245/s10434-019-07309-8

[52] Burris, H.A., Moore, M.J., Andersen, J., Green, M.R., Rothenberg, M.L., Modiano, M.R., *et al.* (1997) Improvements in Survival and Clinical Benefit with Gemcitabine as First-Line Therapy for Patients with Advanced Pancreas Cancer: A Randomized Trial. *Journal of Clinical Oncology*, **15**, 2403-2413. https://doi.org/10.1200/jco.1997.15.6.2403

[53] Cunningham, D., Chau, I., Stocken, D.D., Valle, J.W., Smith, D., Steward, W., *et al.* (2009) Phase III Randomized Comparison of Gemcitabine versus Gemcitabine Plus Capecitabine in Patients with Advanced Pancreatic Cancer. *Journal of Clinical Oncology*, **27**, 5513-5518. https://doi.org/10.1200/jco.2009.24.2446

[54] Cui, J., Qin, S., Zhou, Y., Zhang, S., Sun, X., Zhang, M., *et al.* (2024) Irinotecan Hydrochloride Liposome HR070803 in Combination with 5-Fluorouracil and Leucovorin in Locally Advanced or Metastatic Pancreatic Ductal Adenocarcinoma Following Prior Gemcitabine-Based Therapy (PAN-HEROIC-1): A Phase 3 Trial. *Signal Transduction and Targeted Therapy*, **9**, Article No. 248. https://doi.org/10.1038/s41392-024-01948-4

[55] Ahmad, S.A., Duong, M., Sohal, D.P.S., Gandhi, N.S., Beg, M.S., Wang-Gillam, A., *et al.* (2020) Surgical Outcome Results from SWOG S1505: A Randomized Clinical Trial of mFOLFIRINOX versus Gemcitabine/Nab-Paclitaxel for Perioperative Treatment of Resectable Pancreatic Ductal Ad-Enocarcinoma. *Annals of Surgery*, **272**, 481-486. https://doi.org/10.1097/sla.0000000000004155

[56] Yamada, D., Kobayashi, S., Takahashi, H., Iwagami, Y., Akita, H., Asukai, K., *et al.* (2024) Results of a Randomized Clinical Study of Gemcitabine Plus Nab-Paclitaxel versus Gemcitabine Plus S-1 as Neoadjuvant Chemotherapy for Resectable and Borderline Resectable Pancreatic Ductal Adenocarcinoma (RCT, CSGO-HBP-015). *Annals of Surgical Oncology*, **31**, 4621-4633. https://doi.org/10.1245/s10434-024-15199-8

[57] Humphris, J.L., Chang, D.K., Johns, A.L., Scarlett, C.J., Pajic, M., Jones, M.D., *et al.* (2012) The Prognostic and Predictive Value of Serum CA19.9 in Pancreatic Cancer. *Annals of Oncology*, **23**, 1713-1722. https://doi.org/10.1093/annonc/mdr561

[58] Luo, G., Liu, C., Guo, M., Cheng, H., Lu, Y., Jin, K., *et al.* (2017) Potential Biomarkers in Lewis Negative Patients with Pancreatic Cancer. *Annals of Surgery*, **265**, 800-805. https://doi.org/10.1097/sla.0000000000001741

[59] O'Brien, D.P., Sandanayake, N.S., Jenkinson, C., Gentry-Maharaj, A., Apostolidou, S., Fourkala, E., *et al.* (2015) Serum CA19-9 Is Significantly Upregulated up to 2 Years before Diagnosis with Pancreatic Cancer: Implications for Early Disease Detection. *Clinical Cancer Research*, **21**, 622-631. https://doi.org/10.1158/1078-0432.ccr-14-0365

[60] Rachagani, S., Kumar, S. and Batra, S.K. (2010) Microrna in Pancreatic Cancer: Pathological, Diagnostic and Therapeutic Implications. *Cancer Letters*, **292**, 8-16. https://doi.org/10.1016/j.canlet.2009.11.010

[61] Park, J.Y. (2011) MicroRNAs in Pancreatic Ductal Adenocarcinoma. *World Journal of Gastroenterology*, **17**, 817-827. https://doi.org/10.3748/wjg.v17.i7.817

[62] Zhang, Y., Huang, Z. and Song, B. (2021) Role of Imaging in Evaluating the Response after Neoadjuvant Treatment for Pancreatic Ductal Adenocarcinoma. *World Journal of Gastroenterology*, **27**, 3037-3049. https://doi.org/10.3748/wjg.v27.i22.3037

[63] Soriano, A., Castells, A., Ayuso, C., Ayuso, J.R., de Caralt, M.T., Ginès, M.À., *et al.* (2004) Preoperative Staging and Tumor Resectability Assessment of Pancreatic Cancer: Prospective Study Comparing Endoscopic Ultrasonography, Helical Computed Tomography, Magnetic Resonance Imaging, and Angiography. *American Journal of Gastroenterology*, **99**, 492-501. https://doi.org/10.1111/j.1572-0241.2004.04087.x

[64] White, R.R., Paulson, E.K., Freed, K.S., Keogan, M.T., Hurwitz, H.I., Lee, C., *et al.* (2001) Staging of Pancreatic Cancer before and after Neoadjuvant Chemoradiation. *Journal of Gastrointestinal Surgery*, **5**, 626-633. https://doi.org/10.1016/s1091-255x(01)80105-0

[65] Marchegiani, G., Todaro, V., Boninsegna, E., Negrelli, R., Sureka, B., Bonamini, D., *et al.* (2018) Surgery after FOLFIRINOX Treatment for Locally Advanced and Borderline Resectable Pancreatic Cancer: Increase in Tumour Attenuation on CT Correlates with R0 Resection. *European Radiology*, **28**, 4265-4273. https://doi.org/10.1007/s00330-018-5410-6

[66] Yang, P., Mao, K., Gao, Y., Wang, Z., Wang, J., Chen, Y., *et al.* (2023) Tumor Size Measurements of Pancreatic Cancer with Neoadjuvant Therapy Based on RECIST Guidelines: Is MRI as Effective as CT? *Cancer Imaging*, **23**, Article No. 8. https://doi.org/10.1186/s40644-023-00528-z

[67] Abdelrahman, A.M., Goenka, A.H., Alva-Ruiz, R., Yonkus, J.A., Leiting, J.L., Graham, R.P., *et al.* (2022) FDG-PET Predicts Neoadjuvant Therapy Response and Survival in Borderline Resectable/Locally Advanced Pancreatic Adenocarcinoma. *Journal of the National Comprehensive Cancer Network*, **20**, 1023-1032.e3. https://doi.org/10.6004/jnccn.2022.7041

[68] Therasse, P., Arbuck, S.G., Eisenhauer, E.A., Wanders, J., Kaplan, R.S., Rubinstein, L., *et al.* (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors. *JNCI*: *Journal of the National Cancer Institute*, **92**, 205-216. https://doi.org/10.1093/jnci/92.3.205

[69] Evangelista, L., Zucchetta, P., Moletta, L., Serafini, S., Cassarino, G., Pegoraro, N., *et al.* (2021) The Role of FDG PET/CT or PET/MRI in Assessing Response to Neoadjuvant Therapy for Patients with Borderline or Resectable Pancreatic Cancer: A Systematic Literature Review. *Annals of Nuclear Medicine*, **35**, 767-776. https://doi.org/10.1007/s12149-021-01629-0

[70] Miller, A.B., Hoogstraten, B., Staquet, M. and Winkler, A. (1981) Reporting Results of Cancer Treatment. *Cancer*, **47**, 207-214. https://doi.org/10.1002/1097-0142(19810101)47:1<207::aid-cncr2820470134>3.0.co;2-6

[71] Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., *et al.* (2009) New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). *European Journal of Cancer*, **45**, 228-247. https://doi.org/10.1016/j.ejca.2008.10.026

[72] Baliyan, V., Kordbacheh, H., Parakh, A. and Kambadakone, A. (2017) Response Assessment in Pancreatic Ductal Adenocarcinoma: Role of Imaging. *Abdominal Radiology*, **43**, 435-444. https://doi.org/10.1007/s00261-017-1434-7

[73] Lee, S.M., Katz, M.H.G., Liu, L., Sundar, M., Wang, H., Varadhachary, G.R., *et al.* (2016) Validation of a Proposed Tumor Regression Grading Scheme for Pancreatic Ductal Adenocarcinoma after Neoadjuvant Therapy as a Prognostic Indicator for Survival. *American Journal of Surgical Pathology*, **40**, 1653-1660. https://doi.org/10.1097/pas.0000000000000738

[74] Sell, N.M., Lee, G.C., Fernández-Del Castillo, C., Ferrone, C.R., Warshaw, A.L., Hong, T.S., *et al.* (2020) Evaluation of Pathologic Response on Overall Survival after Neoadjuvant Therapy in Pancreatic Ductal Adenocarcinoma. *Pancreas*, **49**, 897-903. https://doi.org/10.1097/mpa.0000000000001590

[75] Sandini, M., Patino, M., Ferrone, C.R., Alvarez-Pérez, C.A., Honselmann, K.C., Paiella, S., *et al.* (2018) Association between Changes in Body Composition and Neoadjuvant Treatment for Pancreatic Cancer. *JAMA Surgery*, **153**, 809-815. https://doi.org/10.1001/jamasurg.2018.0979