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无法切除的结直肠肝转移患者行放疗加化疗与单纯化疗的比较：Meta分析

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摘　要

目的：本研究旨在评估选择性内放疗加化疗对无法切除的结直肠肝转移患者的疗效。方法：检索Pubmed、CNKI、Embase、Cochrane图书馆中心等电子文献数据库中截至2021年7月发表的文章。以中文和英文撰写的文章均被考虑在内。只选择随机对照试验，通过缓解率、病情进展、无进展生存期和总生存期评价联合治疗的疗效。结果：本研究纳入4个随机对照试验，共报告1238名参与者，其中622名接受选择性内放疗加化疗，616名接受单纯化疗。结果显示，联合治疗的患者客观缓解率较高(RR = 2.04, 95% CI 1.02~4.09, P = 0.04)，进展期较低(RR = 0.36, 95% CI 0.16~0.82, P = 0.02)，无进展生存期(HR = 1.61, 95% CI 0.70~3.72, P = 0.27)和总生存期(HR = 1.22, 95% CI 0.84~1.10, P = 0.29)差异无统计学意义。结论：选择性内放疗对肝脏病灶的短期显著改善并不能转化为长期生存的益处。

关键词

放射治疗，化疗，联合治疗，结直肠癌，肝脏转移

Selective Internal Radiotherapy plus Chemotherapy versus Chemotherapy Alone in Patients with Unresectable Colorectal Liver Metastases: A Meta-Analysis

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Abstract

Objective: This meta-analysis was designed to assess the efficacy of selective internal radiotherapy plus chemotherapy in patients with unresectable colorectal liver metastases. Method: Electronic literature databases including Pubmed, CNKI, Embase and the Cochrane Library Center were searched for articles published till July 2021. The articles written in both Chinese and English were considered. Only randomized controlled trials were selected. Main outcomes (response rate, progressive disease, progression-free survival and overall survival) were evaluated by assessing the efficacy of the combined treatment. Results: Four randomized controlled trials were included in this meta-analysis and a total of 1238 participants were reported (622 treated with selective internal radiotherapy plus chemotherapy and 616 treated with chemotherapy alone). The results showed patients who were treated with combined treatment had higher objective response rate (RR = 2.04, 95% CI 1.02~4.09, P = 0.04), lower progressive disease (RR = 0.36, 95% CI 0.16~0.82, P = 0.02), no significant difference in progression-free survival (HR = 1.61, 95% CI 0.70~3.72, P = 0.27) and overall survival (HR = 1.22, 95% CI 0.84~1.10, P = 0.29). Conclusions: The significant improvement in liver disease control of the addition of selective internal radiotherapy did not translate to a benefit in survival.

Keywords

Radiotherapy, Chemotherapy, Combination Therapy, Colorectal Cancer, Liver Metastases

1. 介绍

结直肠癌是第二常见的恶性肿瘤，每年有超过 100 万的患者被诊断，其中约 40%存在肝转移[1] [2]。肝转移是晚期结直肠癌患者死亡的主要原因。获得手术切除机会的患者可以获得良好的预后，5 年生存率为 30%~40% [3]。但尽管手术技术有了很大的进步，只有 10%~20%的肝局限转移的患者可以得到手术机会[4] [5] [6] [7]。无法切除的肝转移病灶通常伴随肿瘤的进展和疾病的快速扩散，会在短时间内导致死亡。

虽然近十年来结肠癌肝转移的全身治疗取得了显著进展，但 5 年生存率仍低于 10%。在大多数医学治疗中心，运用选择性内放疗治疗肝局限转移病灶被证明有效[8] [9] [10]。选择性内放疗是一种针对肝脏多个疾病部位，利用微球对肝病灶进行电离辐射的近距离放射治疗的技术。因为肝肿瘤的血供主要来源于肝动脉，当微球注入肝动脉后，优先滞留在肝肿瘤的血管丛中[11] [12]。肝肿瘤暴露在足够剂量的电离辐射下，从而使肿瘤体积有效缩小，而正常肝组织则接受低剂量、可耐受的辐射[13] [14]。选择性内放疗联合化疗治疗结直肠癌肝转移的疗效已通过提高客观缓解率、延长无进展生存期得到证实，但未见联合治疗提高患者总生存期的报道[15] [16] [17] [18]。本研究旨在评估选择性内放疗加化疗对无法切除的结直肠肝转移患者的疗效。

2. 材料与方法

2.1. 检索策略

本研究遵循 QUOROM 指南进行，并根据《系统审查和荟萃分析首选报告项目(PRISMA)声明》进行报告。检索 Pubmed、CNKI、Embase、Cochrane 图书馆中心等电子文献数据库中截至 2021 年 7 月发表的文章。我们对语言没有限制。我们使用了以下医学学科标题术语：“结直肠肿瘤”或“结直肠肿瘤”或“结直肠癌”，“肿瘤转移”或“转移”，“肝癌”或“肝癌”，“放疗”或“靶向放疗”，“化疗”。对所有检索到的文献进行回顾，以进一步拓展相关研究。

2.2. 入选标准

本研究遵循以下标准：1) 无法切除的结直肠肝转移患者；2) 两组研究，实验组：选择性内放疗 + 化疗；对照组：单纯化疗；3) 报告有用数据，包括客观缓解率或疾病进展或无进展生存期或总生存期。

2.3. 排除标准

本研究采用以下标准来排除不符合条件的研究：1) 没有可用数据的报告；2) 未报告长期结果；3) 审查文章，评论，病例报告，动物研究。

2.4. 数据处理

从纳入的研究中独立提取了以下数据：第一作者、发表年份、研究类型、参与者数量和特征、治疗结果包括客观缓解率、疾病进展率、无进展生存期、总生存期和安全性。如果需要，可以根据从文章中提取的数据对结果进行重新计算。本研究使用 Review Manager 5.3 进行。计数数据由相对危险度(RR)、风险比(HR)、95%置信区间(95% CI)表示。在本研究中，我们通过 Cochran Q 检验和 I^2 评估异质性。我们认为，如果 I^2 统计量为>50%，并选择随机效应模型，且存在异质性。否则，我们使用固定效应模型来存储数据。$P < 0.05$ 被认为存在显著的差异。

3. 结果

本研究初步搜索出 472 篇文章。大多数文章由于标题和摘要不符合等原因被排除。本研究共审查 86 篇文章，其中 82 篇文章被排除，最后纳入 4 项随机对照试验[19] [20] [21] [22]。总共有 1238 名患者被纳入研究，其中 622 名接受了选择性内放疗加化疗，616 名仅接受了化疗。文献筛选流程见图 1，纳入文献的基本特征见表 1。

Table 1. Basic characteristics of included literature (experimental group/control group)
表 1. 纳入文献的基本特征(实验组/对照组)

作者及年份	方案	患者人数	中位年龄	男性(%)	ORR	PD	PFS (月)	OS (月)
Alain Hendlisz. 2010 [19]	随机对照	44 (21/23)	62/62	48%/78%	85.7%/34.8% P = 0.001	9.5%/60.9%	5.5/2.1 P = 0.003	10.0/7.3 P = 0.80
B. Gray. 2001 [20]	随机对照	70 (36/34)	59/62	78%/76%	44%/17.6% P = 0.01	8.3%/23.5%	15.9/9.7 P = 0.001	23.5/18.4 P = 0.18
Guy van Hazel. 2004 [21]	随机对照	21 (11/10)	64/65	91%/80%	72.2%/0%% P < 0.001	0%/40% P < 0.001	18.6/3.6 P < 0.0005	29.4/12.8 P = 0.025
Harpreet S Wasan. 2017 [22]	随机对照	1103 (554/549)	63/63	66%/66%	72%/63% P = 0.0012	31%/49% P < 0.0001	11.0/10.3 P = 0.11	22.6/23.3 P = 0.61

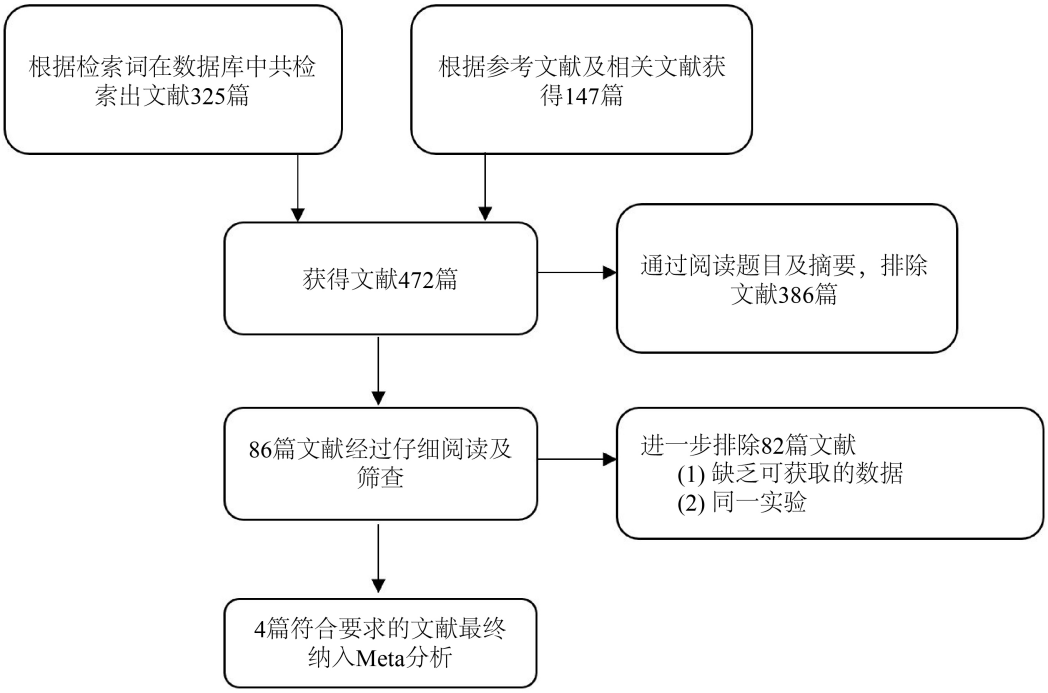

Figure 1. Flow chart of the included studies
图 1. 文献筛选流程图

3.1. 发表偏倚

采用 Cochrane 推荐的改良偏倚风险工具进行评估纳入研究的质量。四项研究报告了充分的随机化(图2)。

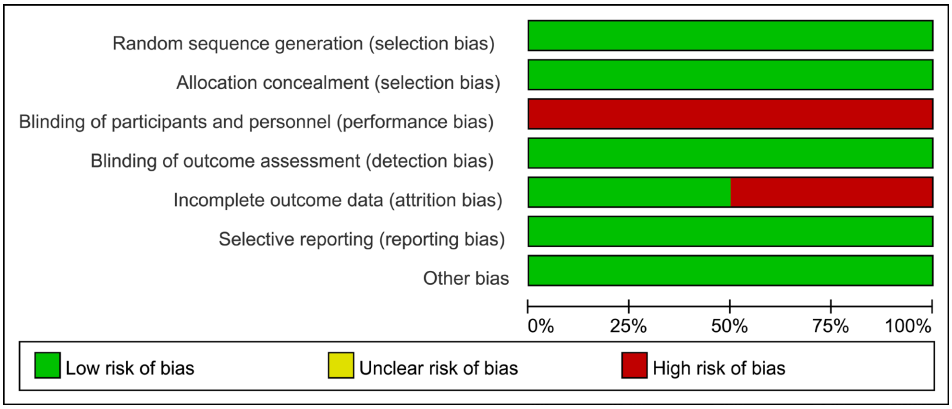

Figure 2. Publication bias
图 2. 发表偏倚

3.2. 客观缓解率

4 项研究[19] [20] [21] [22]评估了 1238 例结肠癌肝转移患者选择性内放疗加化疗对客观缓解率的影响。合并 RR 为 2.04 (95% CI 1.02~4.09，P = 0.04；图 3)，证明选择性内放疗的加入显著提高了客观缓解率。研究之间观察到相当大的异质性(P = 0.003, I^2 = 79%)。

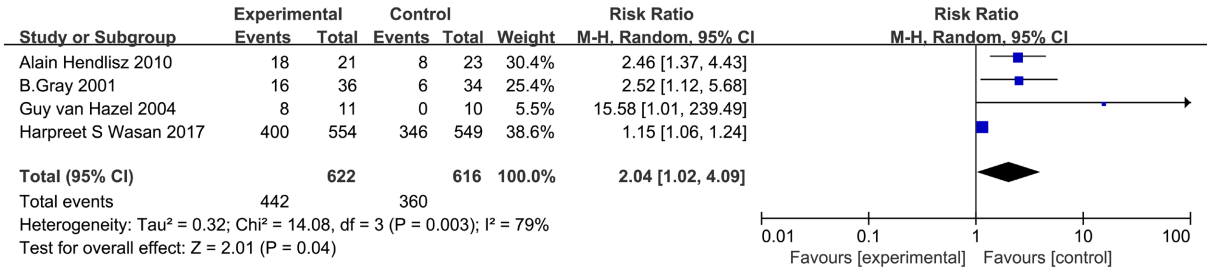

Figure 3. Objective response rate
图 3. 客观缓解率

3.3. 疾病进展

4 项研究[19] [20] [21] [22]确定了选择性内放疗对疾病进展的影响，共 1238 例患者，证实选择性内放疗显著延缓了疾病进展(RR = 0.36，95% CI 0.16~0.82，P = 0.02；图 4)。

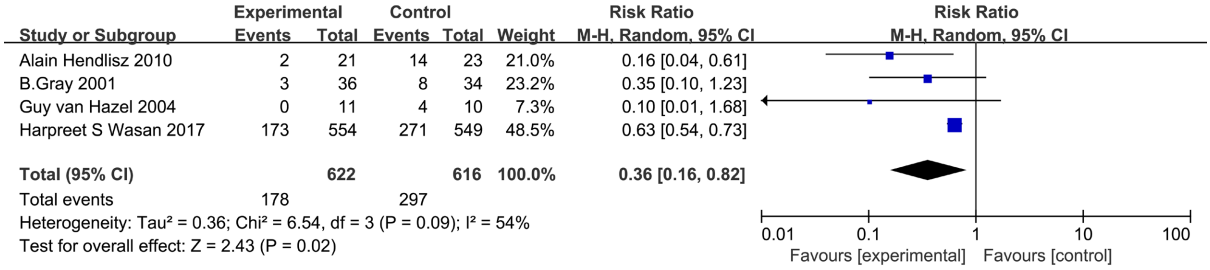

Figure 4. Progressive disease
图 4. 疾病进展

3.4. 无进展生存期

两组共 1147 例患者中，仅有 2 项研究[19] [22]符合评价无进展生存期的条件。其他 2 项研究[20] [21]因未报告 HR 和 95% CI 而被排除。纳入研究的数据显示在表 2 中。两组间无进展生存期估算值差异无统计学意义(HR = 1.61，95% CI 0.70~3.72，P = 0.27；图 5)，而各研究间的异质性较高(P = 0.01, I^2 = 85%)。

Table 2. PFS and OS were in included literature
表 2. 纳入文献的 PFS 及 OS 数据

作者及年份	患者人数(实验组/对照组)	PFS (月)(实验组/对照组)	PFS			OS (月)(实验组/对照组)	OS		
			Hazard radio	95% CI	P-value		Hazard radio	95% CI	P-value
Alain Hendlisz. 2010 [19]	44 (21/23)	5.5/2.1	2.63	1.38~5.0	0.003	10.0/7.3	1.09	0.56~2.13	0.80
B. Gray. 2001 [20]	70 (36/34)	15.9/9.7			0.001	23.5/18.4	1.41	0.86~2.34	0.18
Guy van Hazel. 2004 [21]	21 (11/10)	18.6/3.6			<0.0005	29.4/12.8	3.03	1.09~8.33	0.025
Harpreet S Wasan. 2017 [22]	1103 (554/549)	11.0/10.3	1.11	0.98~1.27	0.11	22.6/23.3	0.96	0.84~1.11	0.61

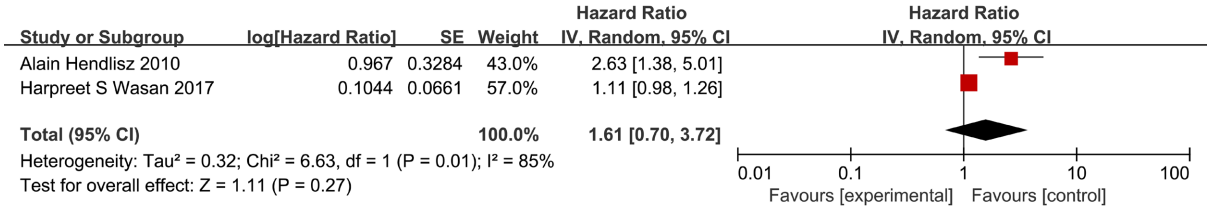

Figure 5. Progression-free survival
图 5. 无进展生存期

3.5. 总生存期

四项研究皆报道了选择性内放疗对总生存期的影响研究[19] [20] [21] [22]，共 1238 例患者。纳入研究的数据显示在表 2 中。总生存期差异无统计学意义(HR = 1.22，95% CI 0.84~1.10，P = 0.29；图 6)，异质性程度中等(P = 0.08, I^2 = 56%)。

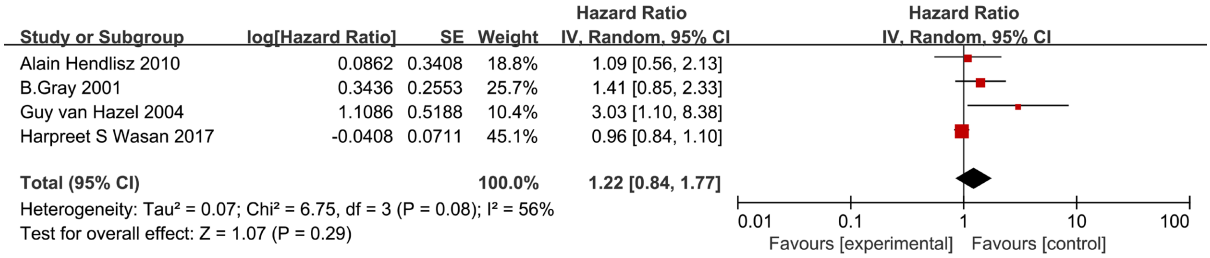

Figure 6. Overall survival
图 6. 总生存期

3.6. 安全性

两组 3~4 级不良事件无差异(表 3)。

Table 3. Adverse reactions and safety (experimental group/control group)
表 3. 不良反应与安全性(实验组/对照组)

作者及年份	不良反应分级		
	1~2	3~4	5
Alain Hendlisz. 2010 [19]	37/34	1/10	
B. Gray. 2001 [20]	300/207	23/23	
Guy van Hazel. 2004 [21]		13/5	
Harpreet S Wasan. 2017 [22]	131/189	365/369	10/11

4. 讨论

手术切除是结直肠肝转移的首选治疗，而选择性内放疗和化疗在治疗结直肠癌肝转移中也起着不可或缺的作用，尤其是对于不能切除的肿瘤。本研究是第一个比较选择性内放疗加化疗和单纯化疗治疗结直肠癌肝转移的研究分析。这项研究显示，接受联合治疗的参与者有更高的客观缓解率，更慢的疾病进展，然而，对肝脏病灶的短期治疗效果的显著改善并没有转化为无进展生存期和总生存期方面的获益。

本研究结果显示，与单纯化疗相比，选择性内放疗+化疗的客观缓解率由 58.4%提高至 71.1% (P = 0.04)。Seza A. Gulec [15]通过对同一个体的左肝和右肝进行比较，发现联合治疗组比单独化疗组产生更好的客观缓解率，肿瘤病灶体积减小(P < 0.01)。本研究结果还显示，与化疗相比，接受选择性放疗加化疗的患者疾病进展从 48.2%下降到 28.6% (P = 0.02)。

研究结果显示无进展生存期(P = 0.27)和总生存期(P = 0.29)差异无统计学意义。3 篇文章分别证明联合治疗可延长肝脏进展时间(P = 0.003; P = 0.001; P < 0.0005) [19] [20] [21] [22]，但是，其中两篇文献因未报告 HR 和 95% CI，未被纳入评估无进展生存期[20] [21]。这一发现与 EORTC clockc 的研究结果形成对比，作者表明疾病短期控制的效果可以使患者的总生存期获益[15]。这种分歧可能与患者不同分期的原位肿瘤或有无肝外转移相关。遗憾的是，我们的研究结果未能显示联合治疗会改善无进展生存期和总生存期。

排除 Harpreet S Wasan 的研究可以消除该研究的异质性[22]。新的结果显示，联合治疗可提高客观缓解率(P < 0.0001)，降低疾病进展(P = 0.0003)，延长总生存期(P = 0.05)。但 3 项研究的参与者较少，且在试验前接受了不同的治疗[19] [20] [21]。因此这一发现需要更多的实验数据和理论分析。

选择性内放疗的不良事件(虚弱、恶心、厌食和肝功能异常)与先前的研究一致[8] [15] [23]。Guy van Hazel [21]和 Harpreet S Wasan [22]报告了联合治疗组有更多的 3~4 级不良反应，特别是中性粒细胞减少和放疗相关的毒性。但增加的不良反应是可预测和可控制的，并没有转化为较低的总生存率。可以得出结论，在化疗中加入选择性内放疗是安全的。

之前的一些研究报道，控制肝脏病灶的进展可以提高手术切除率[24] [25] [26]。然而，Harpreet S Wasan [22]结果表明，有 94 例(17%)联合治疗组患者和 88 例(16%)单纯化疗组患者接受了手术切除。尽管联合治疗改善了肝病灶的客观缓解率，但在切除率并无明显影响(P = 0.67)。导致这种分歧的主要原因是肿瘤是否可切除取决于肝转移病灶的数量和分布。对于有肝外疾病的患者，提高肝的反应率对切除率没有影响。只有当所有肿瘤部位都局限于肝脏时，客观缓解率的改善才会影响切除率。

对于是否可行手术切除，原位肿瘤和肝转移瘤的发展程度都是至关重要的。术前化疗可控制肿瘤进展，增加肿瘤切除的可能性[26] [27]。然而，单纯的化疗不足以控制晚期结直肠癌患者的局部肿瘤病灶。因此术前联合肝脏选择性内放疗是必要的，这已经在以前的研究中得到了验证[28] [29] [30] [31]。在结直肠癌和肝转移同期手术切除后，联合治疗组出现局部复发 5 例(4.7%)，远处转移 74 例(68.9%) [32]，与既往研究一致[33] [34] [35]。

这项研究有几个缺点。首先，纳入研究的患者之间存在差异，患者在试验前可能接受过其他治疗，或者肿瘤进展程度不同。其次，不同研究中，采取的化疗方案有所不同。此外，许多研究还受到样本量小的限制。

5. 结论

本研究结果显示，对于不能切除的结直肠癌肝转移患者，选择性内放疗联合化疗，可以改善客观缓解率和控制疾病进展，但并不能使无进展生存期和总生存期获益。

参考文献

[1] Manfredi, S., Lepage, C., Hatem, C., *et al*. (2006) Epidemiology and Management of Liver Metastases from Colorectal Cancer. *Annals of Surgery*, **244**, 254-259. https://doi.org/10.1097/01.sla.0000217629.94941.cf

[2] Parkin, D.M., Bray, F., Ferlay, J., *et al*. (2005) Global Cancer Statistics, 2002. *CA*: *A Cancer Journal for Clinicians*, **55**, 74-108. https://doi.org/10.3322/canjclin.55.2.74

[3] Nordlinger, B., Van Cutsem, E., Rougier, P., *et al*. (2007) Does Chemotherapy Prior to Liver Resection Increase the

Potential for Cure in Patients with Metastatic Colorectal Cancer? A Report from the European Colorectal Metastases Treatment Group. *European Journal of Cancer*, **43**, 2037-2045.

[4] Berber, E., Pelley, R. and Siperstein, A.E. (2005) Predictors of Survival after Radiofrequency Thermal Ablation of Colorectal Cancer Metastases to the Liver: A Prospective Study. *Journal of Clinical Oncology*, **23**, 1358-1364. https://doi.org/10.1200/JCO.2005.12.039

[5] Van Cutsem, E., Nordlinger, B., Adam, R., *et al*. (2006) Towards a Pan-European Consensus on the Treatment of Patients with Colorectal Liver Metastases. *European Journal of Cancer*, **42**, 2212-2221.

[6] Navarra, G., Ayav, A., Weber, J.C., *et al*. (2005) Short-and-Long Term Results of Intraoperative Radiofrequency Ablation of Liver Metastases. *International Journal of Colorectal Disease*, **20**, 521-528. https://doi.org/10.1007/s00384-005-0743-4

[7] Rothbarth, J. and van de Velde, C.J. (2005) Treatment of Liver Metastases of Colorectal Cancer. *Annals of Oncology*, **16**, ii144-ii149. https://doi.org/10.1093/annonc/mdi702

[8] Kennedy, A.S., Coldwell, D., Nutting, C., *et al*. (2006) Resin ^{90}Y-Microsphere Brachytherapy for Unresectable Colorectal Liver Metastases: Modern USA Experience. *International Journal of Radiation Oncology, Biology, Physics*, **65**, 412-425. https://doi.org/10.1016/j.ijrobp.2005.12.051

[9] Szyszko, T., Al-Nahhas, A., Tait, P., *et al*. (2007) Management and Prevention of Adverse Effects Related to Treatment of Liver Tumours with ^{90}Y Microspheres. *Nuclear Medicine Communications*, **28**, 21-24. https://doi.org/10.1097/MNM.0b013e3280121a8f

[10] Jakobs, T.F., Hoffmann, R.T., Poepperl, G., *et al*. (2007) Mid-Term Results in Otherwise Treatment Refractory Primary or Secondary Liver Confined Tumours Treated with Selective Internal Radiation Therapy (SIRT) Using ^{90}Yttrium Resin-Microspheres. *European Radiology*, **17**, Article No. 1320. https://doi.org/10.1007/s00330-006-0508-7

[11] Campbell, A.M., Bailey, I.H. and Burton, M.A. (2001) Tumour Dosimetry in Human Liver Following Hepatic Yttrium-90 Microsphere Therapy. *Physics in Medicine and Biology*, **46**, 487-498. https://doi.org/10.1088/0031-9155/46/2/315

[12] Kennedy, A., Nag, S., Salem, R., *et al*. (2007) Recommendations for Radioembolization of Hepatic Malignancies Using Yttrium-90 Microsphere Brachytherapy: A Consensus Panel Report from the Radioembolization Brachytherapy Oncology Consortium. *International Journal of Radiation Oncology, Biology, Physics*, **68**, 13-23. https://doi.org/10.1016/j.ijrobp.2006.11.060

[13] Hirata, A., Hirotsu, Y., Nieh, T.G., *et al*. (2007) Direct Imaging of Local Atomic Ordering in a Pd-Ni-P Bulk Metallic Glass Using Cs-Corrected Transmission Electron Microscopy. *Ultramicroscopy*, **107**, 116-123. https://doi.org/10.1016/j.ultramic.2006.06.002

[14] Kennedy, A.S., Nutting, C., Coldwell, D., *et al*. (2004) Pathologic Response and Microdosimetry of (90)Y Microspheres in Man: Review of Four Explanted Whole Livers. *International Journal of Radiation Oncology, Biology, Physics*, **60**, 1552-1563. https://doi.org/10.1016/j.ijrobp.2004.09.004

[15] Gulec, S.A., Pennington, K., Wheeler, J., *et al*. (2013) Yttrium-90 Microsphere-Selective Internal Radiation Therapy with Chemotherapy (Chemo-SIRT) for Colorectal Cancer Liver Metastases: An *in Vivo* Double-Arm-Controlled Phase II Trial. *American Journal of Clinical Oncology*, **36**, 455-460. https://doi.org/10.1097/COC.0b013e3182546c50

[16] Chua, T.C., Bester, L., Saxena, A., *et al*. (2011) Radioembolization and Systemic Chemotherapy Improves Response and Survival for Unresectable Colorectal Liver Metastases. *Journal of Cancer Research and Clinical Oncology*, **137**, 865-873. https://doi.org/10.1007/s00432-010-0948-y

[17] Kosmider, S., Tan, T.H., Yip, D., *et al*. (2011) Radioembolization in Combination with Systemic Chemotherapy as First-Line Therapy for Liver Metastases from Colorectal Cancer. *Journal of Vascular and Interventional Radiology*: *JVIR*, **22**, 780-786. https://doi.org/10.1016/j.jvir.2011.02.023

[18] Cohen, S.J., Konski, A.A., Putnam, S., *et al*. (2014) Phase I Study of Capecitabine Combined with Radioembolization Using Yttrium-90 Resin Microspheres (SIR-Spheres) in Patients with Advanced Cancer. *British Journal of Cancer*, **111**, 265-271. https://doi.org/10.1038/bjc.2014.344

[19] Hendlisz, A., Van den Eynde, M., Peeters, M., *et al*. (2010) Phase III Trial Comparing Protracted Intravenous Fluorouracil Infusion Alone or with Yttrium-90 Resin Microspheres Radioembolization for Liver-Limited Metastatic Colorectal Cancer Refractory to Standard Chemotherapy. *Journal of Clinical Oncology*, **28**, 3687-3694. https://doi.org/10.1200/JCO.2010.28.5643

[20] Gray, B., Van Hazel, G., Hope, M., *et al*. (2001) Randomised Trial of SIR-Spheres Plus Chemotherapy vs. Chemotherapy Alone for Treating Patients with Liver Metastases from Primary Large Bowel Cancer. *Annals of Oncology*, **12**, 1711-1720. https://doi.org/10.1023/A:1013569329846

[21] Van Hazel, G., Blackwell, A., Anderson, J., *et al*. (2004) Randomised Phase 2 Trial of SIR-Spheres Plus Fluorouracil/Leucovorin Chemotherapy versus Fluorouracil/Leucovorin Chemotherapy Alone in Advanced Colorectal Cancer.

Journal of Surgical Oncology, **88**, 78-85. https://doi.org/10.1002/jso.20141

[22] Wasan, H.S., Gibbs, P., Sharma, N.K., *et al*. (2017) First-Line Selective Internal Radiotherapy Plus Chemotherapy versus Chemotherapy Alone in Patients with Liver Metastases from Colorectal Cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): A Combined Analysis of Three Multicentre, Randomised, Phase 3 Trials. *The Lancet Oncology*, **18**, 1159-1171. https://doi.org/10.1016/S1470-2045(17)30457-6

[23] Jakobs, T.F., Hoffmann, R.T., Dehm, K., *et al*. (2008) Hepatic Yttrium-90 Radioembolization of Chemotherapy-Refractory Colorectal Cancer Liver Metastases. *Journal of Vascular and Interventional Radiology*: *JVIR*, **19**, 1187-1195. https://doi.org/10.1016/j.jvir.2008.05.013

[24] Chun, Y.S., Laurent, A., Maru, D., *et al*. (2009) Management of Chemotherapy-Associated Hepatotoxicity in Colorectal Liver Metastases. *The Lancet Oncology*, **10**, 278-286. https://doi.org/10.1016/S1470-2045(09)70064-6

[25] Nordlinger, B., Sorbye, H., Glimelius, B., *et al*. (2008) Perioperative Chemotherapy with FOLFOX4 and Surgery versus Surgery Alone for Resectable Liver Metastases from Colorectal Cancer (EORTC Intergroup Trial 40983): A Randomised Controlled Trial. *The Lancet*, **371**, 1007-1016. https://doi.org/10.1016/S0140-6736(08)60455-9

[26] Folprecht, G., Grothey, A., Alberts, S., *et al*. (2005) Neoadjuvant Treatment of Unresectable Colorectal Liver Metastases: Correlation between Tumour Response and Resection Rates. *Annals of Oncology*, **16**, 1311-1319. https://doi.org/10.1093/annonc/mdi246

[27] Alberts, S.R., Horvath, W.L., Sternfeld, W.C., *et al*. (2005) Oxaliplatin, Fluorouracil, and Leucovorin for Patients with Unresectable Liver-Only Metastases from Colorectal Cancer: A North Central Cancer Treatment Group Phase II Study. *Journal of Clinical Oncology*, **23**, 9243-9249. https://doi.org/10.1200/JCO.2005.07.740

[28] Bujko, K., Nasierowska-Guttmejer, A., Wyrwicz, L., *et al*. (2013) Neoadjuvant Treatment for Unresectable Rectal Cancer: An Interim Analysis of a Multicentre Randomized Study. *Radiotherapy and Oncology*: *Journal of the European Society for Therapeutic Radiology and Oncology*, **107**, 171-177. https://doi.org/10.1016/j.radonc.2013.03.001

[29] Myerson, R.J., Tan, B., Hunt, S., *et al*. (2014) Five Fractions of Radiation Therapy Followed by 4 Cycles of FOLFOX Chemotherapy as Preoperative Treatment for Rectal Cancer. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **88**, 829-836. https://doi.org/10.1016/j.ijrobp.2013.12.028

[30] Radu, C., Berglund, A., Påhlman, L., *et al*. (2008) Short-Course Preoperative Radiotherapy with Delayed Surgery in Rectal Cancer—A Retrospective Study. *Radiotherapy and Oncology*: *Journal of the European Society for Therapeutic Radiology and Oncology*, **87**, 343-349. https://doi.org/10.1016/j.radonc.2007.11.025

[31] van Dijk, T.H., Tamas, K., Beukema, J.C., *et al*. (2013) Evaluation of Short-Course Radiotherapy Followed by Neoadjuvant Bevacizumab, Capecitabine, and Oxaliplatin and Subsequent Radical Surgical Treatment in Primary Stage IV Rectal Cancer. *Annals of Oncology*, **24**, 1762-1769. https://doi.org/10.1093/annonc/mdt124

[32] An, H.J., Yu, C.S., Yun, S.C., *et al*. (2012) Adjuvant Chemotherapy with or without Pelvic Radiotherapy after Simultaneous Surgical Resection of Rectal Cancer with Liver Metastases: Analysis of Prognosis and Patterns of Recurrence. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **84**, 73-80. https://doi.org/10.1016/j.ijrobp.2011.10.070

[33] Assumpcao, L., Choti, M.A., Gleisner, A.L., *et al*. (2008) Patterns of Recurrence Following Liver Resection for Colorectal Metastases: Effect of Primary Rectal Tumor Site. *Archives of Surgery*, **143**, 743-749. https://doi.org/10.1001/archsurg.143.8.743

[34] Kim, T.W., Lee, J.H., Lee, J.H., *et al*. (2011) Randomized Trial of Postoperative Adjuvant Therapy in Stage II and III Rectal Cancer to Define the Optimal Sequence of Chemotherapy and Radiotherapy: 10-Year Follow-Up. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **81**, 1025-1031. https://doi.org/10.1016/j.ijrobp.2010.07.012

[35] Lee, J.H., Lee, J.H., Ahn, J.H., *et al*. (2002) Randomized Trial of Postoperative Adjuvant Therapy in Stage II and III Rectal Cancer to Define the Optimal Sequence of Chemotherapy and Radiotherapy: A Preliminary Report. *Journal of Clinical Oncology*, **20**, 1751-1758. https://doi.org/10.1200/JCO.2002.07.037