·药物安全与合理应用·

恶性肿瘤临床试验中短期中间指标与终点指标相关性 Meta 分析的系统评价

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[摘要]　**目的:**对肿瘤临床试验中短期中间指标[客观缓解率(ORR)、完全缓解(CR)等]与终点指标[无进展生存期(PFS)、总生存期(OS)]相关性研究的 Meta 分析进行系统评价,以探讨不同肿瘤领域下短期中间指标与终点指标的相关性。**方法:**在 Cooper 等(2020)研究基础上,更新检索 2019 年 3 月—2022 年 1 月 Medline,Embase,Cochrane,Web of science 和 CINAHL 数据库,系统评价短期中间指标与终点指标的个体水平与试验水平相关性分析的 Meta 分析,并对研究数量最多的 3 种肿瘤的研究进行亚组分析。**结果:**共纳入 77 篇文献,分析了 20 种不同的肿瘤,其中非小细胞肺癌、结直肠癌和乳腺癌是 3 种最常见的肿瘤类型。相关性分析结果显示,纳入的研究主要分析了 ORR 与 OS(91%)、ORR 与 PFS(35%)之间的关系,无论是在个体水平还是试验水平上,ORR 等短期中间指标与 PFS 和 OS 均无明显的相关性。亚组分析结果显示,在非小细胞肺癌领域,超过一半的研究显示 ORR 与 PFS 在试验水平上的相关性 $R^2>0.4$,两者具有较好或很好的相关性。且在非小细胞肺癌和结直肠癌领域,多数研究显示 ORR 与 PFS 的试验水平相关性($R^2_{NSCLC}>0.3$,$R^2_{CRC}>0.2$)强于 ORR 与 OS($R^2_{NSCLC}>0.1$,$R^2_{CRC}>0.1$)。**结论:**总体而言,ORR 等短期中间指标可能不能成为替代终点指标。另外,在非小细胞肺癌和结直肠癌领域,特别是非小细胞肺癌领域,试验水平上 ORR 可能会成为 PFS 的替代终点指标,是值得监管部门关注的一个短期中间指标。

[关键词]　短期中间指标;终点指标;相关性;系统评价;肿瘤
[中图分类号]　R969.3　　[文献标志码]　A　　[文章编号]　1003－3734(2023)01－0093－10

A systematic evaluation of meta analyses on the correlation between short-term endpoints and final endpoints in cancer

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[**Abstract**]　**Objective**: To summarize the evaluation of meta analyses on the correlation between short-term endpoints (ORR, CR, etc.) and final endpoints (PFS, OS) in cancer, and to explore the correlation between different types of cancer. **Methods**: Based on Cooper et al. (2020), a systematic search in databases of Medline, Embase, the Cochrane library, Web of Science, and CINAHL were updated from March 2019 to January 2022. Meta analyses assessing the individual-level and trial-level correlation between short-term intermediate endpoints and final endpoints are summarized, and subgroup analyses are conducted in terms of the three most common cancer types. **Results**: The systematic review includes 77 studies across 20 types of cancer, in which non small cell lung

[基金项目]　中国博士后科学基金资助项目(2020M681784);2020 年度高校哲学社会科学研究一般项目(2020SJA0070)
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cancer (NSCLC), colorectal cancer (CRC), and breast cancer are the three most common cancer types. The included studies mainly analyzed the correlation between ORR and OS (91%) or PFS (35%), and the correlation was week regardless of individual-level and trial-level. In subgroup analyses, over half studies in NSCLC indicated good or excellent trial-level correlation between ORR and PFS ($R^2 > 0.4$). Also, most studies in NSCLC and CRC indicated that the trial-level correlation between ORR and PFS ($R^2_{NSCLC} > 0.3$, $R^2_{CRC} > 0.2$) was stronger than that between ORR and OS ($R^2_{NSCLC} > 0.1$, $R^2_{CRC} > 0.1$). **Conclusion**: The short-term intermediate endpoints, such as ORR, may not be good surrogates for final endpoints. ORR may be a short-term intermediate indicator worth be noticed by regulators, which could be surrogate for PFS in trial-level in the field of NSCLC and CRC, especially in the field of NSCLC.

[**Key words**] short-term endpoints; final endpoints; correlation; systematic review; cancer

目前,恶性肿瘤是仅次于心血管疾病的全球第二大导致死亡的疾病,已严重威胁人类健康[1]。预估恶性肿瘤将超过心血管疾病成为导致死亡的主要原因[2]。

在抗肿瘤药物的临床试验中,无进展生存期(progression-free survival, PFS)、总生存期(overall survival,OS)是主要疗效终点指标。其中 OS 是体现抗肿瘤药物疗效的金标准[3-4]。然而,目前临床试验选择使用短期中间指标来代替和预测与患者相关最终临床结果的现象越来越常见[5]。

关于短期中间指标的定义,本研究中仅包括基于肿瘤反应的临床指标,即客观缓解率(objective response rate, ORR)、完全缓解(complete response, CR)、部分缓解(partial response,PR)、较好的部分缓解(very good partial response,VGPR)、缓解持续时间(duration of response,DoR)等。

虽然短期中间指标的应用可加快抗肿瘤创新药物的上市,更好惠及恶性肿瘤患者,但短期中间指标和终点指标之间的相关性尚不明确,短期中间指标的获益能否有效代替终点指标仍存有疑问。对于在短期中间指标已显示获益的药物中,仍存在相当部分的药物在后续临床试验中未达到预期效果[6]。因此,对已有的短期中间指标和终点指标相关性分析的 Meta 分析进行系统综述以探究两者之间的相关性具有重要意义。

Copper 等[7](2020)对截至 2019 年 3 月的相关 Meta 分析研究进行系统综述,系统比较了 ORR 等短期中间指标与 PFS, OS 等终点指标的相关性。本文将在 Cooper 等[7](2020)研究基础上进行更新,进一步对相关 Meta 分析研究进行综述,探究短期中间指标(ORR,CR,PR,VGPR,DoR)与终点指标(PFS,OS)的相关性,以评估其能否有效代替终点指标 PFS,OS,并进一步探索不同肿瘤领域下短期中间指标的替代有效性。

资料与方法

1 纳排标准

1.1 纳入标准 ① 公开发表的多个临床试验(包括单臂临床试验与安慰剂对照临床试验)的 Meta 分析或 Meta 回归。② 短期中间指标(ORR,CR,PR,VGPR 或 DoR)与终点指标(PFS,OS)之间的相关性采用相关系数(r,如 Pearson 相关系数或 Spearman 相关系数)和/或决定系数(R^2)表示。③ 同时报告短期中间指标与终点指标的个体水平相关性和试验水平相关性,或仅报告其中一项。④ 疾病领域主要集中在晚期或转移性实体肿瘤。

1.2 排除标准 ① 仅分析单个临床试验或单个队列研究的报告。② 治疗方案为辅助治疗或新辅助治疗的研究。③ 非英文语种研究。④ 重复研究。⑤ 无法获得全文的研究。

1.3 研究对象 对晚期或转移性实体肿瘤短期中间指标和终点指标进行相关性研究的 Meta 分析。

1.4 结局指标 短期中间指标(ORR,CR,PR,VGPR,DoR)与终点指标(PFS,OS)的个体水平相关性和试验水平相关性。

2 检索策略

在 Medline,Embase,Cochrane,Web of science 和 CINAHL 数据库进行检索。检索时间为 2019 年 3 月—2022 年 1 月。检索策略采取主题词和自由词相结合的方式,主题词包括“Neoplasms”,“Regression analysis”等,自由词包括“tumour response”,“duration of response”,“ORR”,“OS”,“correlation”

等。同时,本研究纳入 Cooper 等[7](2020)研究中纳入的 64 项相关研究作为补充分析。以 Embase 数据库为例,具体检索策略示例见表 1。

表 1 Embase 检索策略

检索步骤	检索词
#1	'neoplasm'/exp
#2	cancer * :ti,ab,kw OR neoplasm * :ti,ab,kw OR tumour * :ti,ab,kw OR tumor * :ti,ab,kw OR malignan * :ti,ab,kw OR oncology:ti,ab,kw OR lymphoma * :ti,ab,kw OR sarcoma * :ti,ab,kw OR melanoma * :ti,ab,kw OR myeloma * :ti,ab,kw OR carcinoma * :ti,ab,kw
#3	#1 OR #2
#4	'tumour response * ':ti,ab,kw OR 'tumor response * ':ti,ab,kw
#5	'objective response * ':ti,ab,kw OR orr:ti,ab,kw
#6	'duration of response * ':ti,ab,kw OR dor:ti,ab,kw
#7	'response rate * ':ti,ab,kw
#8	'complete response * ':ti,ab,kw
#9	'overall response * ':ti,ab,kw
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	#3 AND #10
#12	'regression analysis'/exp
#13	regression:ti,ab,kw OR relationship:ti,ab,kw OR correlation:ti,ab,kw OR prediction:ti,ab,kw OR association:ti,ab,kw
#14	#12 OR #13
#15	#11 AND #14
#16	endpoint * :ti,ab,kw OR 'end point * ':ti,ab,kw
#17	surrogate:ti,ab,kw OR surrogacy:ti,ab,kw
#18	#16 OR #17
#19	#15 AND #18
#20	'progression-free survival'/exp
#21	'progression free survival':ti,ab,kw OR pfs:ti,ab,kw
#22	'overall survival':ti,ab,kw OR os:ti,ab,kw
#23	'time to progression':ti,ab,kw OR ttp:ti,ab,kw
#24	#20 OR #21 OR #22 OR #23
#25	#19 AND #24

3 文献筛选

在排除重复文献后,由 2 位研究者独立进行文献筛选、提取资料并交叉核对。首先通过阅读标题和摘要进行初筛,排除明显不相关的文献;对于剩余文献则进一步阅读全文进行复筛,以确定最终是否纳入。

4 数据处理

提取纳入研究中所报告的短期中间指标和终点指标的个体水平相关性和试验水平相关性数据并进行综述,分析短期中间指标与终点指标之间的相关性。其中,个体水平相关性也叫做绝对相关性,指临床试验中某一组患者的短期中间指标与终点指标的相关性,如 ORR 与中位 OS 的相关性;试验水平相关性也叫做疗效相关性,指某一临床试验 2 组患者的相对短期中间指标和终点指标的相关性,如 2 组患者 ORR 的 OR 值与 OS 的 HR 值相关性。受限于数据的可及性,采用 r(包括 Pearson 相关系数和 Spearman 相关系数)衡量个体水平的相关性,R^2 衡量试验水平的相关性。另外,本研究选取研究数量最多的前 3 种肿瘤领域,分析特定疾病亚组中的短期中间指标和终点指标的相关性。

采用医疗质量和效率研究所(IQWiG)标准评价临床中间指标与终点指标的个体水平相关性(r)的强弱:很好($r \geq 0.85$ 或 r 的置信区间下限 ≥ 0.85);好($r \geq 0.85$ 或 $r \geq 0.85$ 且其置信区间下限 < 0.85);一般($0.7 \leq r < 0.85$ 或 $0.7 \leq r$ 的置信区间 < 0.85);差($r < 0.7$ 或 r 的置信区间上限 < 0.7)[7-8]。采用

BSES2 标准评价临床中间指标与终点指标的试验水平相关性(R^2)的强弱:很好($R^2 \geqslant 0.6$);好($0.4 \leqslant R^2 < 0.6$);一般($0.2 \leqslant R^2 < 0.4$);差($R^2 < 0.2$)[7,9]。如纳入研究同时报告了 R^2 的置信区间,则根据其置信区间下限判断相关性的强弱。两者的相关性越强,则短期中间指标越有可能成为替代终点指标。

5 文献质量评价

本研究的文献质量评价基于 AMSTAR-2[10] 和 ReSEEM[11],从中提取出与本研究相关的 8 个关键条目进行质量评价,这 8 个关键条目分别为纳排标准、多数据库检索、重复文献选择、数据提取及核对、偏倚风险评估、适当的相关性分析方法、通过亚组分析判断异质性、不确定性评估[7]。经独立的 2 名评价员依据评判表评估文献内容是否符合标准,符合为“是”、不符合为“否”、未说明为“不清楚”。

结　果

1 文献筛选结果

采用以上检索策略通过数据库获得相关文献 1 555 篇,剔除重复文献 409 篇后剩余 1 146 篇文献。经过文献的初筛和复筛之后,最终剩余 13 篇文献纳入研究[12-24]。另外,本研究从 Cooper 等[7](2020)的研究中获取符合纳排标准的文献 64 篇[25-88],最终共纳入文献 77 篇。文献的具体筛选流程见图 1。

2 质量评价结果

纳入研究的质量评价结果见图 2。

3 纳入研究的基本特征

纳入研究的基本特征见表 2。

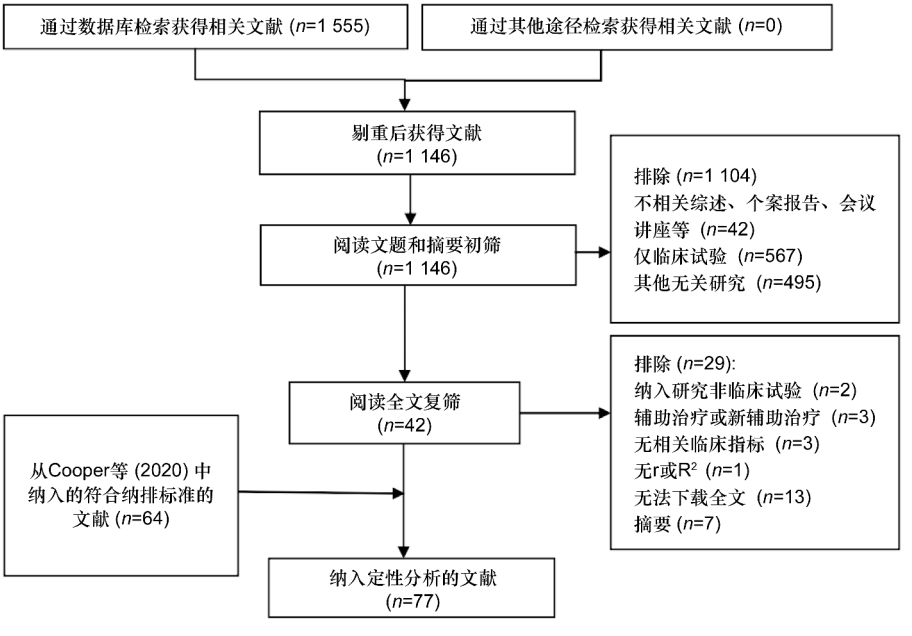

图 1　文献筛选流程图

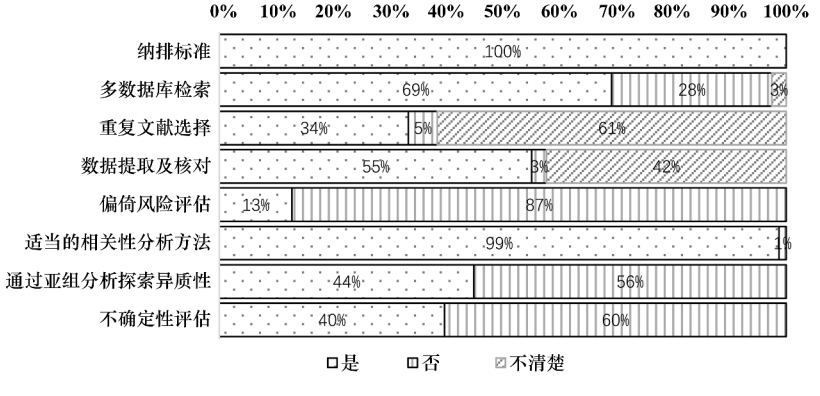

图 2　质量评价结果

表 2 纳入研究的基本特征

项目	例数	占比/%
疾病种类		
NSCLC	20	26
CRC	13	17
BC	5	6
其他	41	53
疾病阶段		
晚期或转移性	55	71
其他	13	17
未说明	9	12
治疗阶段		
一线治疗	26	34
后线或多线治疗	40	52
未提及	11	14
治疗方案		
化疗	22	29
免疫疗法	14	18
靶向疗法	8	10
其他	33	43
相关性分析		
ORR 与 OS	70	91
ORR 与 PFS	27	35
CR 与 OS	8	10
CR 与 PFS	7	9
相关性研究水平		
个体水平	35	45
试验水平	51	66
STE 报告		
是	5	6
否	72	94

NSCLC:非小细胞肺癌;CRC:结直肠癌;BC:乳腺癌;STE:替代阈值效应

4 相关性分析

本研究首先对纳入研究的个体水平和试验水平的相关性结果进行分析,相关性分析结果见表 3。另外,本研究分别对非小细胞肺癌、结直肠癌和乳腺癌 3 个疾病领域的研究根据治疗方案和治疗阶段划分亚组进行分析。在这 3 个疾病领域中,相关研究主要分析了 ORR 与 PFS/OS 之间的相关性。

表 3 相关性分析结果

相关关系	研究数目/项	相关性(r/R^2)	文献来源
个体水平			
ORR vs PFS	12	(-0.72,0.96)	[50,52,60,62-63,67,70-71,73-74,79,85]
ORR vs OS	30	(-0.40,1.00)	[14-15,21,25-27,42,44-45,49,51-52,55,57-60,67-74,76,78-79,82,85]
CR vs PFS	2	(0.22,0.83)	[67,88]
CR vs OS	3	(-0.04,0.62)	[57,67,69]
PR vs PFS	1	(0.35,0.70)	[67]
PR vs OS	1	(0.29,0.66)	[67]
试验水平			
ORR vs PFS	14	(0.02,0.94)	[16,19,22-24,28-29,33-34,52,75,79,83,86]
ORR vs OS	43	(-0.08,0.84)	[12-20,22-24,28-30,32-39,41,43-44,46-48,52-54,61,64-66,68,71,75,80-81,84,86]
CR vs PFS	1	(0.45,0.93)	[77]
CR vs OS	3	(0.05,0.48)	[15,41,43]

4.1 非小细胞肺癌 在个体水平上,共 8 项研究[52,57-58,73,76,78,83,85]分析了 ORR 与 PFS/OS 的相关性。4 项研究[52,73,83,85]分析了 ORR 与 PFS 之间的相关性,其中 2 项研究[52,73]报告了 r,在 0.33 到 1.06 之间(见图 3)。

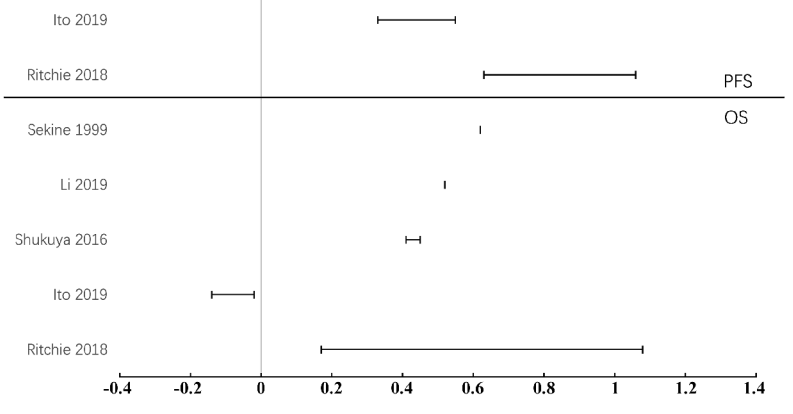

图 3 ORR 与 PFS/OS 的个体水平相关性(r)结果汇总——非小细胞肺癌

2 项研究[52,73]均显示两者的相关性较差。8 项研究[52,57-58,73,76,78,83,85]分析了 ORR 与 OS 之间的相关性,其中 5 项研究[52,57,73,76,78]报告了 r,在 -0.14 到 1.08 之间(见图 3),5 项研究[52,57,73,76,78]均显示两者的相关性较差。

在试验水平上,共 14 项研究[15,17,22-23,28-29,46-47,52-53,66,73,75,84]分析了 ORR 与 PFS/OS 的相关性。8 项研究[22-23,28-29,52,73,75,84]分析了 ORR 与 PFS 之间的相关性,其中 7 项[22-23,28-29,52,75,84]报告了 R^2,在 0.003 到 0.98 之间(见图 4)。在这 7 项研究中,2 项研究[23,75]显示两者相关性较差,1 项研究[22]显示两者相关性一般,2 项研究[28-29]显示两者相关性较好,2 项研究[52,84]显示两者相关性很好。14 项研究[15,17,22-23,28-29,46-47,52-53,66,73,75,84]分析了 ORR 与 OS 之间的相关性,其中 10 项研究[22-23,28-29,47,52-53,66,75,84]报告了 R^2,在 0 到 0.91 之间(见图 4)。在这 10 项研究中,7 项研究[22-23,28-29,47,53,75]显示两者相关性较差,1 项研究[66]显示两者相关性一般,1 项研究[52]显示两者相关性较好,1 项研究[84]显示两者相关性很好。

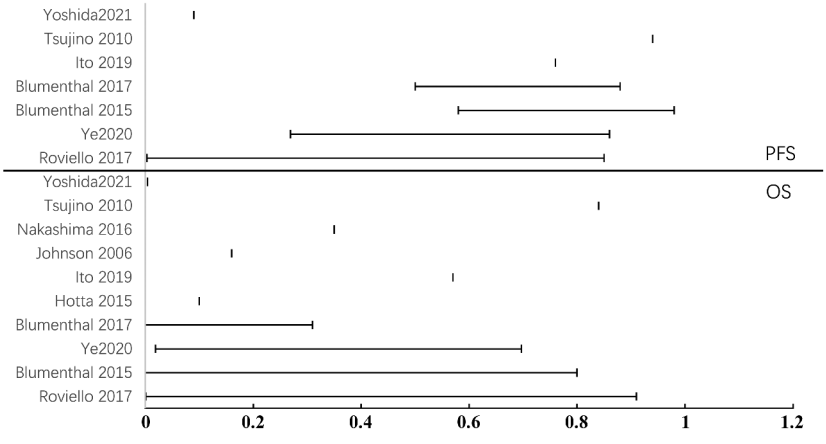

图 4 ORR 与 PFS/OS 的试验水平相关性(R^2)结果汇总——非小细胞肺癌

4.2 结直肠癌 在个体水平上,共 3 项研究[42,60,82]分析了 ORR 与 PFS/OS 的相关性。1 项研究[60]分析了 ORR 与 PFS 之间的相关性并报告了 r,为 0.66,可见两者相关性较差。3 项研究[42,60,82]分析了 ORR 与 OS 之间的相关性并报告了 r,在 0.38 到 0.72 之间,3 项研究[42,60,82]均显示两者的相关性较差。

在试验水平上,共 11 项研究[13,24,32-33,35,38,40,53,80,82,84]分析了 ORR 与 PFS/OS 的相关性。4 项研究[24,33,40,84]分析了 ORR 与 PFS 之间的相关性并报告了 R^2,在 0.23 到 0.87 之间(见图 5)。

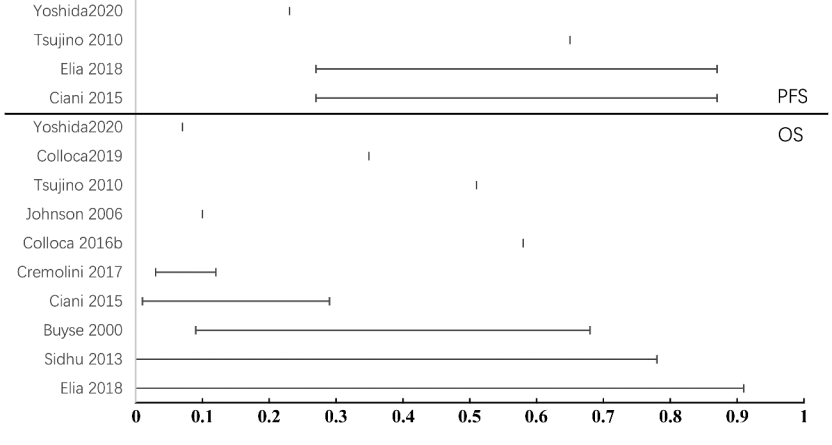

图 5 ORR 与 PFS/OS 的试验水平相关性(R^2)结果汇总——结直肠癌

在这 4 项研究中,3 项研究[24,33,40]显示两者的相关性一般,1 项研究[84]显示两者的相关性很好。11 项研究[13,24,32-33,35,38,40,53,80,82,84]分析了 ORR 与 OS 之间相关性,其中 10 项研究[13,24,32-33,35,38,40,53,80,84]报告了 R^2,在 0 到 0.91 之间(见图 5)。在这 10 项研究中,7 项研究[24,32-33,38,40,53,80]显示两者的相关性较差,1 项研究[13]显示两者的相关性一般,2 项研究[35,84]显示两者的相关性较好。

4.3 乳腺癌 在个体水平上,共 2 项研究[59,72]分析了 ORR 与 PFS/OS 的相关性。其中,未有研究报告 ORR 与 PFS 之间的相关性;2 项研究[59,72]分析了 ORR 与 OS 之间的相关性并报告了 r,在 0.29 到 0.72 之间,2 项研究[59,72]均显示两者的相关性较差。

在试验水平上,共 3 项研究[30-31,43]分析了 ORR 与 PFS/OS 的相关性。1 项研究[31]分析了 ORR 与 PFS 之间的相关性但并未报告 R^2;3 项研究[30-31,43]分析了 ORR 与 OS 之间相关性,其中 2 项研究[30,43]报告了 R^2,在 0 到 0.65 之间。在这 2 项研究中,1 项研究[30]显示两者的相关性较差,1 项研究[43]显示两者的相关性一般。

讨 论

本研究在 Cooper 等[7](2020)研究的基础上对肿瘤领域短期中间指标与终点指标相关性的 Meta 分析进行了系统综述,同时对非小细胞肺癌、结直肠癌和乳腺癌 3 种研究数量最多的肿瘤类型分别进行亚组分析。纳入研究多集中于 ORR 与 PFS/OS 之间相关性的分析,且无论是在个体水平还是试验水平上,ORR 与 PFS/OS 的 r 或 R^2 的范围较广,并无明显的相关性,ORR 等短期中间指标并不能成为 PFS 和 OS 的替代终点指标。亚组分析结果显示,在个体水平上,非小细胞肺癌、结直肠癌和乳腺癌领域的 ORR 与 PFS/OS 的相关性均较差,并不具有疾病特异性;在试验水平上,非小细胞肺癌领域中超过一半的研究显示 ORR 与 PFS 的相关性较好或很好。另外,在非小细胞肺癌领域,多数研究报告的 ORR 与 PFS 试验水平相关性 $R^2>0.3$,多数研究报告的 ORR 与 OS 试验水平相关性 $R^2>0.1$;在结直肠癌领域中,多数研究报告的 ORR 与 PFS 试验水平相关性 $R^2>0.2$,多数研究报告的 ORR 与 OS 试验水平相关性 $R^2>0.1$。可见,在这 2 个疾病领域中,ORR 与 PFS 的试验水平相关性强于 ORR 与 OS。因此,对于治疗非小细胞肺癌和结直肠癌的药品上市,特别是非小细胞肺癌,试验水平上 ORR(如 ORR 的差值、比值比)可能会成为 PFS 的替代终点指标,是值得监管部门关注的一个短期中间指标。

目前,国内并无研究对肿瘤领域的短期中间指标和终点指标相关性的 Meta 分析进行系统综述,相关研究多集中于国外。Savina 等[89](2018)和 Haslam 等[90](2019)探究了肿瘤领域短期中间指标与终点指标之间的相关性,发现 ORR 等短期中间指标与 PFS 和 OS 的相关性较弱。Mauguen 等[91](2013)对晚期肺癌短期中间指标和终点指标相关性的 Meta 分析进行了系统综述,研究发现在可手术切除肺癌的新辅助治疗中,无病生存期(disease-free survival,DFS)与 OS 在个体水平和试验水平上均具有较高的相关性,DFS 可以作为 OS 的替代终点指标,但该研究并未分析晚期肺癌的 ORR 等短期中间指标与 OS 的相关性。Fiteni 等[92](2016)对已发表的乳腺癌短期中间指标和终点指标相关性的 Meta 分析进行了系统综述,发现 ORR 等短期中间指标与 OS 的相关性较差。在本研究中,同样未发现乳腺癌领域中 ORR 与 OS 的相关性。

本研究存在一定的局限性。首先,由于纳入研究数量有限,本研究仅选取了非小细胞肺癌、结直肠癌和乳腺癌 3 种肿瘤类型,其他类型的肿瘤由于相关研究数量较少,未能进行亚组分析。其次,本研究仅对以英文发表的相关 Meta 分析进行了综述,未纳入中文的研究。经检索发现,目前仅有 1 项中文研究分析了化疗药物治疗非小细胞肺癌的短期中间指标 ORR 与终点指标 OS 之间的相关性[93]。研究结果发现,ORR 与 OS 存在相关性,但结果一致性较差[93]。未来,随着短期中间指标和终点指标相关性的 Meta 分析研究不断丰富,可对其进行进一步综述以更加全面分析两者的相关性。

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编辑:蒋欣欣/接受日期:2022 – 05 – 10