Analysis report (Supporting information)

Effect of oral nutritional supplements with or without nutritional counselling on mortality, treatment tolerance, and quality of life in head and neck cancer patients receiving

(chemo)radio therapy: a systematic review and meta-analysis $% \left({{{\bf{n}}_{{\rm{s}}}}} \right)$

Mello et al. (2020)

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1 Abbreviations

CCRT: concurrent chemo-radiotherapy
CI: confidence interval
CT: chemotherapy
MD: mean difference
MID: minimal important difference
NC: nutritional counselling
ONS: oral nutritional supplements
RR: risk ratio
RT: radiotherapy
SD: standard deviation
seTE: standard error
SMD: standardized mean difference
TE: estimated treatment effect
2 Packages

library(meta)

```
## Loading 'meta' package (version 4.9-7).
## Type 'help(meta)' for a brief overview.
library(readr)
library(rmeta)
library(devtools)
```

```
## Loading required package: usethis
```

```
library(robvis)
library(patchwork)
library(ggplot2)
library(tidyr)
```

3 Standard configurations for the meta-analyses

```
settings.meta(hakn = TRUE) # Hartung-Knapp adjustment
Parsed with column specification:
cols(
  .default = col_double(),
  outclab = col_character(),
 D1 = col_character(),
 D2 = col_character(),
 D3 = col_character(),
 D4 = col_character(),
 D5 = col_character(),
  Overall = col_character(),
  bias = col_character(),
  site = col_character(),
  studlab = col_character(),
  X23 = col_logical()
)
```

See $spec(\ldots)$ for full column specifications.

4 Comparison 1

4.1 Mortality

4.1.1 Main analysis

Including only results at most at some concerns of bias.

4.1.1.1 Forest plot



4.1.1.2 Proportion of information at each level of risk of bias



4.1.2 Sensitivity analysis

Including all available results.

4.1.2.1 Forest plot

Warning in qt(1 - alpha/2, df = df): NaNs produzidos

Warning in qt(1 - alpha/2, df = df): NaNs produzidos

	Experim	ental	Co	ntrol					
Study	Events	Total	Events	Total	Risk Ratio	RR		95%-CI	Weight
bias = High risk of bias	6								
Arnold 1989	3	23	0	27		→ 8.17	[0.44;	150.30]	18.0%
Chitapanarux	0	20	1	20		0.33	[0.01;	7.72]	15.6%
bias = Some concerns									
Cereda 2018	5	78	3	81		1.73	[0.43;	7.00]	66.5%
bias = Unknown									
Jiang 2019	0	46	0	45					0.0%
Random effects model Heterogeneity: $l^2 = 7\%$, τ^2	8 = 0.1227	167	4 34	173		1.77	[0.11;	29.48]	100.0%
	···,	μ ο.			01 0.1 0.5 1 2 10	100			
					avours NC + ONS Favours NC ale	one			
					Mortality				

4.1.2.2 Proportion of information at each level of risk of bias



4.1.2.3 Risk of bias assessments by study



4.2 Treatment tolerance

4.2.1 RT Complete suspension

4.2.1.1 Forest plot

Warning: For a single study, inverse variance method used instead of Mantel-## Haenszel method.

Study	Experim Events	ental Total	Co Events	ontrol Total		I	Risk F	Ratio			RR	95%-	CI Weight
bias = Some concerns Cereda 2018 – RT complete suspension	1	78	3	81			-				0.35	[0.04; 3.2	6] 100.0%
bias = Unknown Jiang 2019		50		50									0.0%
Random effects model Heterogeneity: l^2 = NA%, τ^2 = NA, p = NA	1	128	3	131							0.35	[0.04; 3.2	6] 100.0%
					0.01 Favou	0.1 urs NC + RT Con	0.5 1 ONS nplete	2 Favou susp	10 Irs NC a ensior	100 alone N			

4.2.1.2 Proportion of information at each level of risk of bias



4.2.1.3 Risk of bias assessments by study



4.2.2 CT Complete suspension

4.2.2.1 Forest plot

Study	Experim Events	ental Total	Co	ontrol Total	Risk	Ratio	RR	95%-0	l Weight
olday	Lvento	iotui	Lvento	Total	TH3N	Itatio		30 /0 C	i neight
bias = Some concerns Cereda 2018 – CT complete suspension Jiang 2019 – incomplete chemotherapy	1 11	29 50	4 10	32 50			0.28 1.10	[0.03; 2.33 [0.51; 2.36	8] 23.8% 6] 76.2%
Random effects model Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.3170$, $p = 0.2$	12	79	14	82	le-05 0.001 0.1 Favours NC + ONS	1 10 10 Favours N	— 0.79 000 1e+05 NC alone	0 [0.00; 1403.55] 100.0%
					CT Complet	e suspens	sion		

4.2.2.2 Proportion of information at each level of risk of bias



4.2.2.3 Risk of bias assessments by study

				Risk of bia	is domains							
		D1	D2	D3	D4	D5	Overall					
Study	Cereda 2018 - CT complete suspension	+	+	+	+	-	-					
	Jiang 2019 – incomplete chemotherapy	+	+	+	+	-	-					
		Domains: D1: Bias due to randomisation. D2: Bias due to deviations from intended intervention. D3: Bias due to missing data. D4: Bias due to outcome measurement. D5: Bias due to selection of reported result.										

4.2.3 RT interruption >= 5 days

4.2.3.1 Forest plot



4.2.3.2 Proportion of information at each level of risk of bias



4.2.3.3 Risk of bias assessments by study



D5: Bias due to selection of reported result.

4.2.4 RT interruption

4.2.4.1 Forest plot

Study	Experin Events	nental Total	Co Events	ontrol Total	Risk Ratio	RR	95%-CI	
bias = Some concerns Nayel 1992 Cereda 2018	0 32	11 78	5 32	12 81		0.10 1.04	[0.01; [0.71;	1.60] 1.52]
bias = High risk of bias Jiang 2019	4	50	0	50 (0.001 0.01 0.1 1 10 100 1	9.00 000	[0.50;	162.89]
					Favours NC + ONS Favours NC alon RT interruption	e		

4.2.4.2 Proportion of information at each level of risk of bias



4.2.4.3 Risk of bias assessments by study



4.2.5 Incomplete CCRT

4.2.5.1 Forest plot



4.2.5.2 Proportion of information at each level of risk of bias



4.2.5.3 Risk of bias assessments by study



4.2.6 RT Dose reduction

4.2.6.1 Forest plot

Study	Experim Events	nental Total	C Events	ontrol Total		Risk Ra	tio		RR	95%-CI
bias = Low risk of bias Cereda 2018 – RT dose reduction	1	78	6	81		•			0.17	[0.02; 1.4]
					0.01 0.1 Favours NC RT	0.5 1 2 + ONS Fa Dose rec	10 avours NC duction	100 alone		

4.2.6.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.6.3 Risk of bias assessments by study



4.2.7 CT Dose reduction

4.2.7.1 Forest plot

Study	Experim Events	ental Total	Co Events	ontrol Total		Ri	isk Ra	tio		RR	95%–Cl
bias = Low risk of bias Cereda 2018 – CT dose reduction	6	29	14	32		•]	0.47	[0.21; 1.07]
					0.2 Favour	0.5 s NC + O	1 NS Fa	2 avours N	5 C alone		
						CEDC	ose rec	duction			

4.2.7.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.7.3 Risk of bias assessments by study



4.2.8 Mucositis (severe)

4.2.8.1 Forest plot



4.2.8.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.8.3 Risk of bias assessments by study



4.2.9 Mucositis (overall)

4.2.9.1 Forest plot

Study	Experin Events	nental Total	Co Events	ontrol Total			Ris	sk Ra	atio			RR	95%–Cl	Weight
bias = High risk of bias														
Cereda 2018	71	78	78	81				+				0.95	[0.87; 1.03]	69.7%
Nayel 1992	9	11	12	12			-					0.82	[0.60; 1.12]	29.3%
Chitapanarux	1	20	4	20	←	+						0.25	[0.03; 2.05]	1.0%
Random effects model	2	109		113			<	\Rightarrow				0.90	[0.58; 1.39]	100.0%
Heterogeneity: $I^2 = 37\%$, τ	² = 0.0152	2, p = 0).21		01	0.2	0.5	1	2	5	10			
					Fav	ours N	0.5 C + ON	SF	avours	NC al	one			
							M	ucosi	tis					

4.2.9.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.9.3 Risk of bias assessments by study



4.2.10 Radiation dermatitis

4.2.10.1 Forest plot



4.2.10.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.10.3 Risk of bias assessments by study

				Risk of bia	s domains	-					
		D1	D2	D3	D4	D5	Overall				
Ŋ	Chitapanarux 2016	X	+	X	X	X	X				
Sti	Jiang 2019	X									
Domains: D1: Bias due to randomisation. D2: Bias due to deviations from intended intervention. D3: Bias due to missing data. D4: Bias due to outcome measurement. D5: Bias due to selection of reported result.											

4.2.11 Nausea

4.2.11.1 Forest plot



4.2.11.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.11.3 Risk of bias assessments by study



4.2.12 Dry mouth

4.2.12.1 Forest plot



4.2.12.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.12.3 Risk of bias assessments by study



4.2.13 Swallowing difficulty

4.2.13.1 Forest plot



4.2.13.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.13.3 Risk of bias assessments by study



4.2.14 Taste and appetite changes

4.2.14.1 Forest plot



4.2.14.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.2.14.3 Risk of bias assessments by study



- 4.2.15 Summary of treatment tolerance outcomes
- 4.2.15.1 Results of meta-analysis

Number of Studies	Interaction P-value	Random Effects Model (Risk Ratio)	RR	9	5%–CI
2 2 ² = 0.3170, p =	= 0.22	<	> 0.79	[0.00; 14	03.55]
1 3 = 0, p = 0.53	0.79		0.77 0.68	[0.37; [0.25;	1.59] 1.86]
3 2 ² = 0.0152, p =	= 0.21	+	0.90	[0.58;	1.39]
2 = 0, p = 0.45		+	1.04	[0.50;	2.17]
2 = 0, p = 0.52		0.01 0.1 0.5 1 2 10 1 Favours NC + ONS Favours NC alone	1.00 7 00	[0.48;	2.10]
	Number of Studies $2^{2} = 0.3170, p =$ $1^{3}_{3} = 0, p = 0.53$ $2^{2} = 0.0152, p =$ $2^{2}_{3} = 0, p = 0.45$ $2^{3}_{4} = 0, p = 0.45$	Number of Interaction Studies P-value $2^{2} = 0.3170, p = 0.22$ 1 0.79 3 0.79	Number of Interaction Studies Random Effects Model (Risk Ratio) 2 2 2 1 2 1 1 0.79 3 1 2 1 3 1 2 1 3 1 2 1 1 1 2 1 1 1 1 1 2 <t< td=""><td>Number of Interaction Studies Random Effects Model (Risk Ratio) RR 2 $(Risk Ratio)$ RR 2 $(Risk Ratio)$ 0.79 1 0.79 0.77 3 0.79 0.77 $0.p = 0.53$ 0.68 2 0.90 $2^{2} = 0.0152, p = 0.21$ 0.90 2 0.90 2 $0.1052, p = 0.21$ 2 0.01 0.1 0.1 0.51 2 0.01 0.1 0.51 1.00 0.01 0.1 0.51 2 0.01 0.1 0.51 2 0.01 0.1 0.51 100 Favours NC + ONS Favours NC alone 100</td><td>Number of Interaction Studies Random Effects Model (Risk Ratio) RR 94 2 $(Risk Ratio)$ RR 94 1 0.79 $[0.00; 14]$ 3 0.79 $[0.00; 14]$ 3 0.77 $[0.37;$ 3 0.90 $[0.58;$ 2 0.90 $[0.58;$ 2 1.04 $[0.50;$ 2 0.9 1.04 $[0.48;$ 2 0.9 1.00 $[0.48;$ 0.01 0.1 0.51 2 1.00 $[0.48;$</td></t<>	Number of Interaction Studies Random Effects Model (Risk Ratio) RR 2 $(Risk Ratio)$ RR 2 $(Risk Ratio)$ 0.79 1 0.79 0.77 3 0.79 0.77 $0.p = 0.53$ 0.68 2 0.90 $2^{2} = 0.0152, p = 0.21$ 0.90 2 0.90 2 $0.1052, p = 0.21$ 2 0.01 0.1 0.1 0.51 2 0.01 0.1 0.51 1.00 0.01 0.1 0.51 2 0.01 0.1 0.51 2 0.01 0.1 0.51 100 Favours NC + ONS Favours NC alone 100	Number of Interaction Studies Random Effects Model (Risk Ratio) RR 94 2 $(Risk Ratio)$ RR 94 1 0.79 $[0.00; 14]$ 3 0.79 $[0.00; 14]$ 3 0.77 $[0.37;$ 3 0.90 $[0.58;$ 2 0.90 $[0.58;$ 2 1.04 $[0.50;$ 2 0.9 1.04 $[0.48;$ 2 0.9 1.00 $[0.48;$ 0.01 0.1 0.51 2 1.00 $[0.48;$

4.2.15.2 Results of structured reporting (no meta-analysis)

Subgroup	Number of Studies	Interaction P-value	Random Effects Mode (Risk Ratio)	RR	95%–Cl
RT suspension Some concerns Unknown Heterogeneity: not applicab	1 0 le			0.35	[0.04; 3.26]
RT interruption >= 5 day Low risk of bias Heterogeneity: not applicab	/S 1 le		+	1.14	[0.69; 1.88]
Incomplete CCRT High risk of bias Heterogeneity: not applicab	1 le			0.37	[0.12; 1.21]
RT dose reduction Low risk of bias Heterogeneity: not applicab	1 le			0.17	[0.02; 1.40]
CT dose reduction Low risk of bias Heterogeneity: not applicab	1 le			0.47	[0.21; 1.07]
Nausea High risk of bias Heterogeneity: not applicab	1 le		-	0.76	[0.42; 1.40]
Swallowing difficulties High risk of bias Heterogeneity: not applicab	1 le		-	0.79	[0.53; 1.18]
Taste and appetite chan High risk of bias Heterogeneity: not applicab	iges 1 le		0.01 0.1 0.5 1 2 10	0.99	[0.77; 1.28]
			Favours NC + ONS Favours NC	alone	

Study	Experim Events	nental Total	Co Events	ontrol Total			Risk Rati	0		RR		95%–CI
bias = Some concerns Nayel 1992 Cereda 2018	0 32	11 78	5 32	12 81	~		<u>_</u>			0.10 1.04	[0.01; [0.71;	1.60] 1.52]
bias = High risk of bias Jiang 2019	4	50	0	50				-		9.00	[0.50;	162.89]
					0.01 Favo	0.1 ours NC + R ⁻	0.5 1 2 ONS Fav T interrupt	10 ours NC ion	100 alone			

4.3 Quality of life (end of treatment)

4.3.1 Global quality of life

4.3.1.1 Forest plot



MIDs for the global health status (QL) scale for improvement (deterioration) were QL: 5.4 (- 6.5) and SF: 4.9 (- 7.7) in head and neck cancer patients (shaded area)

Musoro J, Coens C, Fiteni F, et al. Evidence-based approach to determine meaningful change in scores of the EORTC QLQ-C30 in breast and head and neck cancer: on behalf of the EORTC Breast, Head and Neck and Quality of Life Groups. 25th annual conference of the international society for quality of life research, Dublin, Ireland. Qual Life Res 2018;27 (Suppl 1): ab101.4, 18. https://doi.org/10.1007/s11136-018-1946-9

4.3.1.2 Proportion of information at each level of risk of bias



4.3.1.3 Risk of bias assessments by study



4.3.2 Sensitivity analysis

Excluding Jiang 2019, because mean and standard deviation for this study were inputted (as described in the methods section of the primary report).

4.3.2.1 Forest plot

	Ex	perim	ental		Co	ntrol											
Study	Total	Mean	SD	Total	Mean	SD		Ν	lean	Differ	ence)		MD	9	5%-CI	Weight
bias = High risk of bias																	
Cereda 2018	67	55.30	28.3	69	53.80	28.5		-		-				1.50	[-8.05;	11.05]	52.8%
Chitapanarux 2016	20	78.00	11.8	20	76.00	19.8		-		•				2.00	[–8.09;	12.09]	47.2%
Random effects model Heterogeneity: $l^2 = 0\% \tau^2$	87	= 0 94		89			[]		1		>	-1		1.74	[–1.44	; 4.91]	100.0%
	- 0, p -	- 0.04					-15	-10	-5	0	5	10	15				
						Fa	ours N	IC alor	ne Far	vours	NC + C	ONS					
									Qua	lity of	life						

4.3.2.2 Proportion of information at each level of risk of bias



4.3.2.3 Risk of bias assessments by study



4.3.3 Quality of life subscales

4.3.3.1 Appetite loss

	E	perim	ental		Co	ntrol		Stand	lardised	Mean			
Study	Total	Mean	SD	Total	Mean	SD		0	Differenc	е		SMD	95%-CI
bias = High risk of bias													
Cereda 2018	67	27.4	31.3	69	30.4	30.8						-0.1	[-0.4; 0.2]
Chitapanarux 2016	20	16.0	5.4	20	23.0	5.4		•				-1.3	[-1.9; -0.6]
							-2	-1	0	1	2		

Favours NC + ONS Favours NC alone

4.3.3.2 Cognitive

Study	E> Total	kperim Mean	ental SD	Total	Co Mean	ntrol SD		St	anda Dif	rdiseo fferen	d Me ce	ean		SMD	95	%–Cl
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20	89.0 97.0	16.6 2.9	69 20	88.0 92.0	18.7 2.9				+				0.1 1.7	[-0.3 [0.9	; 0.4] ; 2.4]
							-3	-2	-1	0	1	2	3			

Favours NC alone Favours NC + ONS

4.3.3.3 Constipation

Study	Ex Total	perim Mean	ental SD	Total	Co Mean	ntrol SD	Standa Di	ardised M ifference	lean	SME	95%-CI	Weight
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20	24.3 5.0	28.8	69 20	20.0 5.0	31.2				0.4	[-0.2; 0.5]	100.0% 0.0%
Random effects model Heterogeneity: $I^2 = NA\%$, τ	87 2 ² = NA	, p = N/	Ą	89			 -0.5	0	0.5	0. 1	[-0.2; 0.5]	100.0%

4.3.3.4 Diarrhoea

	E	cperime	ental		Co	ntrol		S	tandaro	dised N	lean			
Study	Total	Mean	SD	Total	Mean	SD			Diff	erence			SMD	95%-CI
bias = High risk of bias														
Cereda 2018	67	4.1	12.8	69	3.0	11.5			-				0.1	[-0.2; 0.4]
Chitapanarux 2016	20	0.0	17.2	20	17.0	17.2			•	_			-1.0	[-1.6; -0.3]
							-2		-1	0	1	2		
							Fav	ours N	IC + ONS	S Favou	irs NC a	lone		

4.3.3.5 Dyspnoea

	E	kperim	ental		Co	ntrol		Stand	ardised	Mean			
Study	Total	Mean	SD	Total	Mean	SD		D	oifference	9		SMD	95%–CI
bias = High risk of bias													
Cereda 2018	67	13.1	28.9	69	8.9	22.4						0.2	[-0.2; 0.5]
Chitapanarux 2016	20	0.0	2.0	20	2.0	2.0		•	_			-1.0	[-1.6; -0.3]
•								1	1				
							-2	-1	0	1	2		
							Favo	urs NC + C	NS Favo	ours NC a	lone		

4.3.3.6 Emotional

Study	Ex Total	operimo Mean	ental SD	Total	Co Mean	ntrol SD	Standardised Mean Difference	SMD	95%–Cl	Weight
bias = High risk of bias							1			
Cereda 2018	67	72.0	23.0	69	75.3	28.2		-0.1	[-0.5; 0.2]	77.3%
Chitapanarux 2016	20	91.0	4.6	20	90.0	4.6		0.2	[-0.4; 0.8]	22.7%
Random effects model Heterogeneity: $I^2 = 0\%$, τ^2	87	- 0 35		89				-0.1	[–1.9; 1.8]	100.0%
Therefore the transformation $T = 0.0, t$	– 0, <i>p</i> -	- 0.55					-4 -2 0 2 4			

4.3.3.7 Fatigue

	E>	perim	ental		Co	ntrol									
Study	Total	Mean	SD	Total	Mean	SD		Ν	lean	Diffe	renc	е		MD	95%-CI
bias = High risk of bias	67	21.0	20.0	60	20 F	25.0								2.4	[70.110]
Chitapanarux 2016	67 20	10.0	29.8 3.4	69 20	29.5 15.0	25.8 3.4	_							2.4 -5.0	[-7.0; 11.8] [-7.1; -2.9]
							-15	-10	-5	0	1 5	10	ı 15		
							Favo	ours NC	C + ON	S Fa	vours	NC al	one		

MID: 12.0 (deteriorate)

Musoro J, Coens C, Fiteni F, et al. Minimally important differences for interpreting EORTC QLQ-C30 scores in melanoma, breast cancer and head and neck cancer patients on behalf of the EORTC breast, Head and Neck, Melanoma and Quality of life groups. ISPOR Europe 2018 Barcelona, November, 2018.

4.3.3.8 Financial

	Ex	perim	ental		Co	ntrol	Standardised Mean			
Study	Total	Mean	SD	Total	Mean	SD	Difference	3MD	95%-CI	Weight
bias = High risk of bias										
Cereda 2018	67	7.7	16.8	69	6.5	17.3	- <u>+</u> -	0.1	[-0.3; 0.4]	77.6%
Chitapanarux 2016	20	18.0	7.3	20	15.0	7.3		0.4	[-0.2; 1.0]	22.4%
Random effects model Heterogeneity: $I^2 = 0\%$, τ^2	87 = 0, <i>p</i> =	= 0.36		89				0.1	[–1.6; 1.9]	100.0%

4.3.3.9 Insomnia

	E	perim	ental		Co	ntrol		S	tanda	rdise	d Me	an			
Study	Total	Mean	SD	Total	Mean	SD			Dif	ferer	nce			SMD	95%–Cl
bias = High risk of bias															
Cereda 2018	67	30.3	32.6	69	20.8	29.6					-			0.3	[0.0; 0.6]
Chitapanarux 2016	20	3.0	2.1	20	0.0	2.1	—					-		1.4	[0.7; 2.1]
							-3	-2	-1	0	1	2	3		
							Favo	ours N	C + ON	IS Fa	avours	NC ald	one		

4.3.3.10 Nausea

Study	E) Total	kperimo Mean	ental SD	Total	Co Mean	ntrol SD		Stand D	ardised M ifference	ean	SM	D	95%–Cl
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20	10.5 12.0	22.4 4.4	69 20	9.0 8.0	20.3 4.4	-2 Favo	–1 ours NC + C	0 NS Favou	1 rs NC alor	0 0 2 ne	.1 .9	[–0.3; 0.4] [0.2; 1.5]

4.3.3.11 Pain

Study	E) Total	operim Mean	ental SD	Total	Co Mean	ntrol SD		Sta	andaro Diffe	dised I erence	Mean		SMD	95%–CI
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20	26.3 9.0	34.2 3.8	69 20	27.6 13.0	27.2 3.8	Г	•]	-0.0 -1.0	[–0.4; 0.3] [–1.7; –0.4]
							-2	-'	1	0	1	2		
							Fave	ours NC	+ ONS	Favo	urs NC a	alone		

4.3.3.12 Physical

	E	cperim	ental		Co	ntrol										
Study	Total	Mean	SD	Total	Mean	SD		ľ	Mean I	Diffe	renc	е		MD	959	%–Cl
bias = High risk of bias																
Cereda 2018	67	74.1	28.6	69	78.1	23.4			•	_				-4.0	[-12.8;	4.8]
Chitapanarux 2016	20	95.0	4.3	20	91.0	4.3				-				4.0	[1.3;	6.7]
								I	I			I				
							-15	-10	-5	0	5	10	15			
							Fav	Jours N	IC alone	e Fa	avours	NC +	ONS			

MID: -7.3 (deteriorate)

4.3.3.13 Role

Study	E Tota	xperi I Mea	ment in S	al D T	otal I	Co Mean	ntrol SD		Star	nda Dif	rdise ferei	ed Me nce	an		SMD	ę	95%–CI
bias = High risk of bia Cereda 2018 Chitapanarux 2016	as 67 20	7 70.) 98.	.8 35 .0 6	.2 .8	69 20	70.5 93.0	33.8 6.8	-2	-1	-	 	-	 I 1	 2	0.0 0.7	[–([().3; 0.3]).1; 1.4]
								Favo	ours NC	alor	ne F	avours	NC + 0	ONS			
4.3.3.14 Social	Exp	erime	ntal		C	ontrol											
Study	Total N	lean	SD 1	Total	Mear	n SD		Me	ean Di	ffere	ence		M)	95%	-CI	Weight
bias = High risk of bias Cereda 2018 Chitapanarux 2016	67 20	87.8 2 89.0	23.3 3.6	69 20	93.1 98.0	17.4) 3.6			*	-			-5.3 -9.0	3 [-) [-1	12.2; 1.3; –	1.6] 6.7]	9.6% 90.4%
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	87 = 0, p = 0	0.32		89			-30	-20 -	-10 0		10	20 3	- 8. 0	6 [-2	22.5;	5.2]	100.0%

MIDs for the social functioning (SF) scale for improvement (deterioration) were SF: 6.1 (- 7.3) in HNC

Musoro J, Coens C, Fiteni F, et al. Evidence-based approach to determine meaningful change in scores of the EORTC QLQ-C30 in breast and head and neck cancer: on behalf of the EORTC Breast, Head and Neck and Quality of Life Groups. 25th annual conference of the international society for quality of life research, Dublin, Ireland. Qual Life Res 2018;27 (Suppl 1): ab101.4, 18. https://doi.org/10.1007/s11136-018-1946-9

4.4 Functional status (end of treatment)

4.4.1 Forest plot



4.4.2 Proportion of information at each level of risk of bias



4.4.3 Risk of bias assessments by study



4.5 Body weight (end of treatment)

4.5.1 Main analysis

Including only results at most at some concerns of bias.

4.5.1.1 Forest plot



4.5.1.2 Proportion of information at each level of risk of bias



4.5.2 Sensitivity analysis 1

Including all available results.

4.5.2.1 Forest plot

Study	Total	Total	ΤE	seTE		Mear	n Differe	nce		MD	95	%–CI	Weight
bias = High risk of bias	5												
Arnold 1989	23.00	27.00	-0.05	1.2						-0.05	[-2.33;	2.23]	12.1%
Chitapanarux 2016	20.00	20.00	6.00	2.9					\rightarrow	6.00	0.25;	11.75	2.1%
Nayel 1992	11.00	12.00									L ,		0.0%
bias = Low risk of bias													
Cereda 2018	78.00	81.00	1.30	0.6			-			1.30	[0.20;	2.40]	37.1%
bias = Some concerns													
Jiang 2019	47.00	48.00	0.97	0.4			+			0.97	[0.10;	1.84]	48.6%
Random effects model										1.08	[-0.45;	2.61]	100.0%
Heterogeneity: $I^2 = 24\%$, τ^2	² = 0.18	391, p =	0.26		[I	1	I			• •	-	
					-10	-5	0	5	10				
					Favou	urs NC ald	one Favo	ours NC +	ONS				
					Bod	ly weigh	t (end of	treatme	ent)				

4.5.2.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



4.5.2.3 Risk of bias assessments by study

				Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
	Arnold 1989	X	X	+	+	-	X
	Cereda 2018	+	+	+	+	+	+
Study	Chitapanarux 2016	X	+	X	+	-	X
	Jiang 2019	+	+	+	+	-	<u> </u>
	Nayel 1992	$\overline{}$	+	+	+	X	X
		Domains: D1: Bias due to randomi	isation				Judgement
		D2: Bias due to deviation	ns from intended interven	tion.			X High
		D3: Bias due to missing D4: Bias due to outcome	data. e measurement.				 Some concerns
		D5: Bias due to selection	n of reported result.				+ Low

4.5.3 Sensitivity analysis 2

Excluding Chitapanarux 2016, because mean and standard deviation for this study were inputted (as described in the methods section of the primary report).

4.5.3.1 Forest plot

Study	Total	Total	TE	seTE		Mear	n Differe	nce		MD	95%-CI	Weight
bias = High risk of bias												
Arnold 1989	23.00	27.00	-0.05	1.2						-0.05	[-2.33; 2.23]	8.2%
Nayel 1992	11.00	12.00	•									0.0%
bias = Low risk of bias												
Cereda 2018	78.00	81.00	1.30	0.6			-			1.30	[0.20; 2.40]	35.2%
bias = Some concerns												
Jiang 2019	47.00	48.00	0.97	0.4			+			0.97	[0.10; 1.84]	56.6%
Random effects model										1.00	[-0.06: 2.07]	100.0%
Heterogeneity: $l^2 = 0\% \tau^2$	- 0 n -	- 0 58				1		1			[0.00, 1.0.]	1001070
	– 0, <i>p</i> –	- 0.50			-10	-5	0	5	10			
					Favo	urs NC ald	one Favo	ours NC	+ ONS			
Body weight (end of treatment)												

4.5.3.2 Proportion of information at each level of risk of bias



4.5.3.3 Risk of bias assessments by study



4.6 Adverse effects

4.6.1 Forest plot

Study	Experim Events	iental Total	Co Events	ntrol Total	Risk Ratio	RR	95%-CI	Weight
bias = High risk of bias	5							
Cereda 2018	9	78	0	81		19.72	[1.17; 333.18]	33.9%
Chitapanarux 2016	7	20	0	20		15.00	[0.91; 246.20]	34.6%
Jiang 2019	3	50	0	50		7.00	[0.37; 132.10]	31.4%
Nayel 1992	0	11	0	12				0.0%
Random effects model Heterogeneity: $l^2 = 0\%$, τ^2	19 = 0, <i>p</i> = 0	159 0.87	0	163		12.95	[3.48; 48.19]	100.0%
0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,				C	0.001 0.01 0.1 1 10 100 100	0		
					Favours NC + ONS Favours NC alone			
			۵ ۸		offecte (neurope vemiting feeling of	fullmon	~)	

Adverse effects (nausea, vomiting, feeling of fullness)

4.6.2 Proportion of information at each level of risk of bias



4.6.3 Risk of bias assessments by study



5 Comparison 2

- 5.1 Mortality
- 5.1.1 Forest plot



5.1.2 Proportion of information at each level of risk of bias



5.1.3 Risk of bias assessments by study



5.2 Quality of life (end of treatment)

5.2.1 Global quality of life

5.2.1.1 Forest plot



5.2.1.2 Proportion of information at each level of risk of bias



5.2.1.3 Risk of bias assessments by study



- 5.2.2 Quality of life subscales
- 5.2.2.1 Appetite loss



5.2.2.2 Constipation



5.2.2.3 Diarrhoea



5.2.2.4 Nausea



5.2.2.5 Pain



5.3 Body weight (end of treatment)

5.3.1 Forest plot



Moriarty 1981 measured body weight but only reported the result as statistically non-significant, so it could not be included in a meta-analysis.

5.3.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



5.3.3 Risk of bias assessments by study



6 Comparison 3

6.1 Mortality

6.1.1 Forest plot



6.1.2 Proportion of information at each level of risk of bias



6.1.3 Risk of bias assessments by study



6.2 Interruption of treatment

6.2.1 Forest plot



6.2.2 Proportion of information at each level of risk of bias



6.2.3 Risk of bias assessments by study



6.3 Summary of non-hematological toxicity outcomes

6.3.1 Forest plot

	Experim	nental	Co	ontrol			
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-Cl
bias = High risk of bias							
Harada 2019 – mucositis (grades 3–4)	3	25	16	25	← + − − −	0.19	[0.06; 0.56]
Harada 2019 – mucositis (grades 1–2)	22	25	9	25		2.44	[1.42; 4.20]
Ravasco 2005 – anorexia (grade 1)	9	25	9	25		1.00	[0.48; 2.09]
Ravasco 2005 – anorexia (grade 2)	5	25	7	25		0.71	[0.26; 1.95]
Ravasco 2005 – dysguesia (grade 1)	10	25	11	25		0.91	[0.47; 1.75]
Ravasco 2005 – dysguesia (grade 2)	11	25	12	25		0.92	[0.50; 1.67]
Ravasco 2005 – nausea/vomiting (grade 1)	3	25	3	25		· 1.00	[0.22; 4.49]
Ravasco 2005 – nausea/vomiting (grade 2)	2	25	2	25		— 1.00	[0.15; 6.55]
Ravasco 2005 – odynophagia/dysphagia (grade 1)	12	25	12	25		1.00	[0.56; 1.78]
Ravasco 2005 – odynophagia/dysphagia (grade 2)	10	25	12	25		0.83	[0.44; 1.56]
Ravasco 2005 – xerostomia (grade 1)	10	25	10	25		1.00	[0.51; 1.97]
Ravasco 2005 – xerostomia (grade 2)	6	25	7	25		0.86	[0.34; 2.19]
Ravasco 2005 - permanent xerostomia and/or taste alterations	12	17	10	13	· · · · · · · ·	0.92	[0.60; 1.41]
					0.1 0.2 0.5 1 2	5 10	
					Eavours ONS Eavours ad	lihtum diet	

Non-hematological toxicity

6.3.2 Proportion of the summary at each level of risk of bias



6.3.3 Risk of bias assessments by study

				Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
	Harada 2019 – mucositis (grades 3–4)	X	+	+	X	-	X
	Harada 2019 – mucositis (grades 1–2)	X	+	+	X	-	X
	Ravasco 2005 – anorexia (grade 1)	+	+	+	X	—	X
	Ravasco 2005 – anorexia (grade 2)	+	+	+	X	-	X
	Ravasco 2005 – dysguesia (grade 1)	+	+	+	X	-	X
	Ravasco 2005 – dysguesia (grade 2)	+	+	+	X	—	X
Study	Ravasco 2005 – nausea/vomiting (grade 1)	+	+	+	X	-	X
	Ravasco 2005 – nausea/vomiting (grade 2)	+	+	+	X	-	X
	Ravasco 2005 – odynophagia/dysphagia (grade 1)	+	+	+	X	—	X
	Ravasco 2005 – odynophagia/dysphagia (grade 2)	+	+	+	X	—	X
	Ravasco 2005 - xerostomia (grade 1)	+	+	+	X	$\overline{}$	X
	Ravasco 2005 – xerostomia (grade 2)	+	+	+	X	-	X
	Ravasco 2005 – permanent xerostomia and/or taste alterations	+	X	X	X	-	X
		Domains:				J	udgement

Domains: D1: Bias due to randomisation. D2: Bias due to deviations from intended intervention. D3: Bias due to missing data. D4: Bias due to outcome measurement. D5: Bias due to selection of reported result.

nent X High Some concerns

+ Low

6.4 Body weight (end of treatment)

6.4.1 Forest plot

	Experimental			Control										
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference					MD	95%-CI	
bias = High	risk of	bias												
Harada 2019	25	48.80	12.3	25	46.90	9.8				•			1.90	[-4.27; 8.07]
							10	5			I F	10		
						_	-10	3-			5	10		
						Fa	avours	ad libt	um diet	Favo	urs ONS			
							Body weight (end of treatment)							

6.4.2 Proportion of information at each level of risk of bias

Risk of bias assessments are weighted by the relative contribution of each study to the meta-analysis result (when applicable)



6.4.3 Risk of bias assessments by study



7 Comparison 4

7.1 Mortality

7.1.1 Forest plot



7.1.2 Proportion of information at each level of risk of bias



7.1.3 Risk of bias assessments by study



7.2 Summary of non-hematological toxicity outcomes

7.2.1 Forest plot

	Experimental		Co	ontrol				
Study	Events	Total	Events	Total	Risk Ra	tio	RR	95%-CI
bias = High risk of bias								
Ravasco 2005 – anorexia (grade 1)	9	25	10	25		_	0.90	[0.44; 1.83]
Ravasco 2005 – anorexia (grade 2)	5	25	2	25			÷ 2.50	[0.53; 11.70]
Ravasco 2005 – dysguesia (grade 1)	10	25	10	25			1.00	[0.51; 1.97]
Ravasco 2005 – dysguesia (grade 2)	11	25	7	25		•	1.57	[0.73; 3.39]
Ravasco 2005 – nausea/vomiting (grade 1)	3	25	4	25			0.75	[0.19; 3.01]
Ravasco 2005 – nausea/vomiting (grade 2)	2	25	1	25		• •	· 2.00	[0.19; 20.67]
Ravasco 2005 - odynophagia/dysphagia (grade 1)	12	25	14	25			0.86	[0.50; 1.46]
Ravasco 2005 – odynophagia/dysphagia (grade 2)	10	25	8	25			1.25	[0.59; 2.64]
Ravasco 2005 – xerostomia (grade 1)	10	25	12	25		-	0.83	[0.44; 1.56]
Ravasco 2005 – xerostomia (grade 2)	6	25	3	25			2.00	[0.56; 7.12]
Ravasco 2005 - permanent xerostomia and/or taste alterations	12	17	10	19		-	1.34	[0.79; 2.27]
						1 1	1	
					0.1 0.2 0.5 1	2 5 1	0	
					Favours ONS Fa	avours NC		
					Non-hematolog	ical toxicity		

7.2.2 Proportion of the summary at each level of risk of bias



7.2.3 Risk of bias assessments by study

		Risk of bias domains									
		D1	D2	D3	D4	D5	Overall				
	Ravasco 2005 – anorexia (grade 1)	+	+	+	×	-	×				
	Ravasco 2005 – anorexia (grade 2)	+	+	+	×	-	×				
	Ravasco 2005 – dysguesia (grade 1)	+	+	+	×	-	X				
	Ravasco 2005 – dysguesia (grade 2)	+	+	+	×	-	×				
	Ravasco 2005 – nausea/vomiting (grade 1)	+	+	+	×	-	×				
Study	Ravasco 2005 – nausea/vomiting (grade 2)	+	+	+	×	-	×				
	Ravasco 2005 – odynophagia/dysphagia (grade 1)	+	+	+	×	$\overline{}$	×				
	Ravasco 2005 – odynophagia/dysphagia (grade 2)	+	+	+	×	$\overline{}$	×				
R	Ravasco 2005 – xerostomia (grade 1)	+	+	+	×	-	×				
	Ravasco 2005 – xerostomia (grade 2)	+	+	+	×	-	×				
	Ravasco 2005 - permanent xerostomia and/or taste alterations	+	×	X	×	$\overline{}$	×				
		Domains:				J	udgement				

Domains: D1: Bias due to randomisation. D2: Bias due to deviations from intended intervention. D3: Bias due to missing data. D4: Bias due to outcome measurement. D5: Bias due to selection of reported result.

X High Some concerns

+ Low