Article type : Consensus Statement

CDI-01075-2019.R1
Original Article

Management strategies for patients with advanced rectal cancer and liver metastases using modified Delphi methodology: results from the PelvEx collaborative

PelvEx Collaborative

Corresponding Authors:
Michael E. Kelly
Centre of Colorectal Disease
St Vincent's University Hospital
Elm Park
Dublin 4, Ireland
+353 1 221 4000

School of Medicine, University College Dublin, Ireland
Kellym11@tcd.ie
@PelvExGroup

Keywords:

Rectal Cancer

Liver metastasis

Survival Outcomes

Surgical Outcomes

International Collaboration

Word Count: 2,194

All authors declare no conflict of interest

All co-authors have seen and approved this submission

Figures and Tables to be printed in black & white

No funding disclosure relevant

Abstract

Background:A total of 15-20% of patients with rectal cancer patients have liver metastases on presentation. The management of these patients is controversial. Heterogeneity in management strategies is considerable, and often dependent on local resources and available expertise.

Methods: members of the *PelvEx Collaborative* were invited to participate in the generation of a consensus statement on the optimal management of patients with advanced rectal cancer with liver involvement. Fifteen statements were created for topical discussion on diagnostic and management issues. Panellists were asked to vote on statements and anonymous feedback was given. A collaborative meeting was used to discuss any nuances and clarify any obscurity. Consensus was considered when >85% agreement on a statement was achieved.

Results: a total of 135 participants were involved in the final round of the Delphi questionnaire. Nine of the fifteen statements reached consensus regarding the management of patients with advanced rectal cancer and oligometastatic liver disease.
Routine use of MRI Liver was not recommended for patients with locally advanced rectal cancer, unless there was concern for metastatic disease on initial Computed Tomography

staging scan. Induction chemotherapy was advocated as first-line treatment in those with synchronous liver metastases in locally advanced rectal cancer. In the presence of symptomatic primary disease, a diverting stoma may be required to facilitate induction chemotherapy. Overall, only one-quarter of the panelists would consider simultaneous pelvic exenteration and liver resection.

Conclusion: this Delphi highlights the diverse treatment of advanced rectal cancer with liver metastases and provides recommendations from an experienced international group regarding the multidisciplinary management approach.

Introduction

The management of metastatic rectal cancer has evolved significantly over the last two decades [1-2]. Historically, surgical resection in patients with advanced rectal cancer has been confined to those without extra-pelvic metastatic disease [3]. However, emerging evidence shows a survival benefit in selected patients that undergo resection of oligometastatic liver disease [4]. Patients with colorectal cancer who present with or develop metastatic disease can be divided into two management groups [5], those considered resectable or potentially resectable after conversion therapy, and those with definitively unresectable disease for whom a palliative approach is most appropriate [6]. Better staging and use of induction chemotherapeutics have helped risk stratify patients into those with good and bad cancer biology subgroups, but this is an imperfect process [7] and debate continues regarding the optimal management sequence and aggressiveness of surgery [8]. Although, synchronous locally advanced rectal cancer with liver metastases is associated with worse prognosis, long-term cure is still possible in selected patients with five-year survival rates of 30-50% reported in several small series [9-12].

Most published studies that have addressed management of colorectal liver metastases are of heterogenous groups combining colonic and rectal neoplasms in one entity [8, 13-14]. In addition, there are few data pertaining to resection of colorectal liver metastases in the setting of locally advanced colorectal cancer invading other pelvic organs. Simultaneous resection

has been sporadically reported, especially when technically feasible (low-volume, favourable disease), in patients that have good performance status [15]. However, to-date, there is no international consensus or guidance on the optimal management of these complex cases. . The aim of this study was to develop an international consensus on the management of advanced rectal cancer with synchronous liver metastases using a modified Delphi consensus methodology in the hope that this might help improve patient outcomes. pic.

Methods:

A Delphi study was conducted to seek international opinion and consensus on the role of pelvic exenteration and simultaneous liver resection in the setting of advanced rectal cancer with synchronous liver metastasis. This process took place from March to August 2019. Those sampled were specialist colorectal/surgical oncology surgeons/physicians from thirty-one countries across six continents. All participants are members of the *PelvEx Collaborative*, established in 2015 to provide large-volume 'real-world' data to ascertain factors associated with outcomes following exenterative surgery. The collaborative is open to any institution/unit that provides a tertiary referral service and care for the management of advanced pelvic cancer[16-17].

Study Questionnaire

The study questionnaire was generated using statements that reflected recent publications and recommendations. Initially, there were eleven questions with an option for participants to suggest further pertinent questions that could be included in subsequent rounds. Respondents completed the online questionnaire via TypeForm® survey website for all four rounds of the Delphi process. A completion date for each round was set and an email reminder was sent to remind non-responders. The first round of the questionnaire assessed surgical preferences and practices regarding management of advanced pelvic cancer necessitating pelvic exenteration in the setting of oligometastatic disease. It was conducted

from 21 March to 19 April 2019. Consensus was considered significant if there was >85% preference for a particular choice. Statements that had <40% preference were not continued into the next round. Subsequent questions were modified to reflect prior round voting, with feedback of choices and removal of low ranked options.

Participants were again invited to partake in round 2. Three new questions were added from participant suggestions after the round 1 voting. Email reminders were again sent to encourage completion. The second round of the questionnaire was conducted from 28 April to 10 May 2019. A process as outlined above was again performed. The third round of voting took place prior to the international *PelvEx Collaborative* meeting in Dublin in June 2019 at which the results were discussed. Subsequently a final round of online voting (9 to 19 August 2019) was performed, to reflect discussions at the meeting.

Results:

In total, 172 surgeons were invited to participate. 149 responded to round 1 (86.6%), with 143 (83.1%) and 140 (81.4%) responding to rounds 2 and 3 respectively. At the international collaborative meeting, 96 participants discussed results of rounds 1-3 voting. After dissemination of meeting discussions, the final round of voting had 135 participants.

Rounds 1 - 3

In Round 1, of the eleven statements, there was no consensus regarding any item. Low ranking options were removed, with three new questions added. Round 2 had no consensus over 85%, however six statements had >75% preferences. Again, low ranking options were removed and results disseminated to participants. Round 3 observed consensus (>85%) in six statements.

PelvEx Collaborative Meeting and Final Round

The *PelvEx Collaborative* meeting facilitated discussion regarding the nuances of each of the statements and clarified language issues and/or management options. Feedback from this meeting was distributed to all panellists. The final round (Round 4) observed consensus (>85%) in nine of fifteen statements (Table 1).

Discussion:

The stimulus for this modified Delphi consensus was to address the global differences surrounding the management of colorectal liver metastases in the setting of advanced rectal cancer. To date, the management of advanced rectal cancer with liver metastasis is very varaible, [18-19]. Many patients undergo palliative treatment without being discussed at an advanced cancer multidisciplinary meeting [20]. Patients presenting with synchronous liver metastasis in the setting of advanced rectal cancer have less favourable cancer biology and poorer survival than those with metachronous liver metastasis. This view is overwhelmingly supported by this Delphi questionnaire. Nevertheless, the referral of these patients for a second opinion at a tertiary unit with specialised input can help select those in whom surgical resection is feasible, with acceptable morbidity, mortality and survival benefit [4, 21].
This modified Delphi questionnaire highlights the nuances and the need for a tailored approach. The routine use of MRI liver in patients with locally advanced rectal cancer is not advocated with a consensus that it should be reserved for those with suspicious abnormalities on CT-TAP. Similarly, e there was no consensus that PET-CT should be performed prior to considering pelvic exenteration on patients with liver metastases. However, a major cofounder is the ready ne availability of MRI Liver and PET-CT at different institutions. Many centres only perform these routinely when involved in a clinical trial. Interestingly, one-fifth of panellists thought that PET-CT rarely influences surgical planning.

There was consensus that induction chemotherapy should be offered to patients and this reflects recent literature [22-24]. In the setting of symptomatic disease such as obstruction or fistulation due to local invasion, the majority recommended a diverting stoma before commencing chemotherapy on the basis that this mightdownstage non-resectable or borderline resectable tumours and increase R0 resection margin rates [25-26]. Additionally, a diverting stoma was indicated in those patients with adverse tumour biology in whomit was considered that disease progression was inevitable during therapy. [27].

This study found that only 25% of participants would routinely consider simultaneous pelvic exenteration and liver resection: 10% would never consider this an option and the the remainder considered synchronous resection only suitable if a limited liver resection with favourable localization was evident.

Whilst improved surgical and anaesthetic techniques may facilitate simultaneous pelvic exenteration and liver resection, these procedures constitute a major undertaking. Additional limiting factors include access to hepatobiliary services and having ample operative time. It is notable that 10% of panellists would never consider this an option. Finally, as expected the majority of participants would recommend adjuvant therapy, even following R0 resection. Length of treatment did not reach consensus, and there remains lack of international consensus on the type of adjuvant therapy [28].

This Delphi questionnaire provides a broad international opinion on best management practice for a challenging problem for which there is a paucity of evidence. The *PelvEx* collaborative members have considerable expertise in the management of advanced rectal cancer and their consensus on specific topics offers guidance while acknowledging a relative lack of evidence.

Conclusion:

This study highlights the diverse management strategies for patients with advanced rectal cancer all liver metastases. It provides recommendations from an experienced international group regarding the multidisciplinary management approach for a challenging problem for which there is remains a paucity of evidence.

References:

1. van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clin Exp Metastasis. 2015;32:457-465
2. Choti MA, Sitzmann JV, Tiburi MF, Sumetochoyimetha W, Rangsin R, Schulick RD et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235:759-766
3. Nielsen M, Rasmussen P, Lindegaard J, Laurberg S. A 10-year experience of total pelvic exenteration for primary advanced and locally recurrent rectal cancer based on a prospective database. Colorectal Dis. 2012;14:1076-1083
4. PelvEx Collaborative. Simultaneous pelvic exenteration and liver resection for rectal cancer with synchronous oligometastatic disease: Results from the *PelvEx Collaborative*. *2019; In Press*

5. Mantke R, Schimdt U, Wolff S, Kube R, Lippert H. Incidence of synchronous liver metastases in patients with colorectal cancer in relationship to clinic-pathologic characteristics. Results of a German prospective multicentre observational study. Eur J Surg Oncol. 2012;38(3):259-265
6. Lutz MO, Zalcberg JR, Glynne-Jones R, Ruers T, Ducreux M, Arnold D et al. Second St. Gallen European Organization for research and treatment of cancer gastrointestinal cancer conference: consensus recommendations on controversial issues in primary treatment of rectal cancer. Eur J Cancer. 2016;63:11-24
7. Pathak S, Nunes QM, Daniels IR, Smart NJ, Poston GJ, Pahlman L. Rectal cancer with synchronous liver metastases: Do we have a clear direction? EJSO. 2015;41:1570-1577
8. Kranse R et al. Trends in incidence, treatment and survival of patients with Stage IV colorectal cancer: a population-based series. Colorectal Dis. 2012;14:56-61
9. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, Hess K, Curley SA. Recurrence and outcomes following hepatic resection, radiofrequency ablation and combined resection/ablation for colorectal liver metastasis. Ann Surg. 2004;239(6):818-825
10. deJong MC, Pulitano C, Ribero D, Strub J, Mentha G, Schulick RD, Choti MA, Aldrighetti L, Capussotti L, Pawlik TM. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg. 2009;250(3):440-448
11. Simmonds PC, Primrose JN, Colquitt JL et al. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer. 2006;94:982-999
12. Mavros MN, de Jong M, Dogeas E, Hyder O, Pawlik TM. Impact of complications on long-term survival after resection of colorectal liver metastases. Br J Surg. 2013;100(5):711-718
13. Martin RC, Augenstein V, Reuter NP, Scoggins CR, McMasters KM. Simultaneous versus staged resection for synchronous colorectal liver metastases. J Am Coll Surg. 2009;208(5):842-850

14. Feng Q, Wei Y, Zhu D et al. Timing of hepatectomy for resectable synchronous colorectal liver metastases: for whom simultaneous resection is more suitable – a meta-analysis. PLoS One. 2014;9(8):e104348

15. Kelly ME, Spolverato G, Le GN, Mavros MN, Doyle F, Pawlik TM, Winter DC. Synchronous colorectal liver metastasis: a network meta-analysis review comparing classical, combined and liver-first strategies. J Surg Oncol 2015;111(3):341-351

16. PelvEx Collaborative. Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer: Results From an International Collaboration. Ann Surg. 2019;269(2):315-32

17. PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. Br J Surg. 2018;105(6):650-657

18. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008;13(1):51-64

19. Gelsomino F, Spallanzani A, Garajova I. The treatment of rectal cancer with synchronous liver metastases: A matter of strategy. Crit Rev Oncol Haematol. 2019;139:91-95

20. Abelson JS, Michelassi F, Sun T, Mao J, Milsom J, Samstein B, Sedrakyan A, Yeo HL. Simultaneous resection for synchronous colorectal liver metastasis: the new standard of care? J Gastrointest Surg. 2017;21(6):975-982

21. Slesser AAP, Bhangu A, Brown G, Mudan S, Tekkis PP. The management of rectal cancer with synchronous liver metastases: a modern surgical dilemma. Tech Coloproctol. 2013;17:1-12

22. Hu KY, Simpson MT, Blank JJ, Szabo A, Eastwood D, Ludwig KA, Peterson CY, Ridolfi TJ.Use of Neoadjuvant Chemotherapy in the Treatment of Locally Advanced Rectal Cancer. J Surg Res. 2019 Nov;243:447-452.

23. Yoo RN, Kim HJ.Total neoadjuvant therapy in locally advanced rectal cancer: Role of systemic chemotherapy.Ann Gastroenterol Surg. 2019 Apr 29;3(4):356-367

24. Petrelli F, Trevisan F, Cabiddu M, Sgroi G, Bruschieri L, Rausa E, Ghidini M, Turati L. Total Neoadjuvant Therapy in Rectal Cancer: A Systematic Review and Meta-analysis of Treatment Outcomes. Ann Surg. 2019 Jul 15. doi: 10.1097/SLA.0000000000003471.

25. Muangkaew P, Cho JY, Han HS, Yoon YS, Choi Y, Jang JY et al. Outcomes of simultaneous major liver resection and colorectal surgery for colorectal liver metastases. J Gastrointest Surg. 2016;20:554-563

26. Pawlik TM, Choti MA. Surgical therapy for colorectal metastases to the liver. J Gastrointest Surg. 2007;11:1057-1077

27. Oliveira RC, Alexandrino H, Cipriano MA, Tralhão JG. Liver Metastases and Histological Growth Patterns: Biological Behavior and Potential Clinical Implications-Another Path to Individualized Medicine? J Oncol. 2019 Feb 25;2019:6280347.

28. Gavriilidis P, Tobias A, Sutcliffe RP, Azoulay D, Roberts KJ.Network Meta-Analysis of Adjuvant Chemotherapy following Resection of Colorectal Liver Metastases.Gastrointest Tumors. 2018 Sep;5(1-2):21-31.

STATEMENT	FINAL ROUND OPTIONS	PERCENTAGE CONSENSUS
What is the correct definition of synchronous liver metastasis	Diagnosed at same time as rectal primary	* 87.4%
	Diagnosed within 3-month	12.6%
Synchronous liver metastasis in the setting of advanced rectal cancer has less favorable cancer biology and poorer survival than	Yes	* 91.8%

metachronous liver metastasis	Unsure	8.2%
MRI liver should be performed in all patients considered for pelvic exenteration (locally advanced and recurrent rectal cancer) prior to undertaking exenteration	Only if there are concerns on routine staging	* 87.3%
	Yes	12.7%
PET-CT should be performed in all patients considered for pelvic exenteration (recurrent rectal cancer) prior to undertaking exenteration	Yes	73.9%
	Only if there are concerns on routine staging	26.1%
How often does routine use of PET-CT for preoperative assessment change the surgical plan?	Sometimes	78.4%
	Rarely	21.6%
In a patient with asymptomatic and resectable *locally advanced rectal cancer* requiring pelvic exenteration, who also has liver metastasis, what would your first treatment be:	Induction chemotherapy	* 88.1%
	Short course radiotherapy, then systemic chemotherapy – then liver resection – then exenteration	11.9%
In a patient with symptomatic and resectable *locally advanced rectal cancer* requiring pelvic exenteration, who also has liver metastasis, what would your first treatment be:	Defunctioning stoma - then induction chemotherapy - then re-assess	* 86.6%
	Defunctioning stoma - then short-course radiotherapy followed by chemotherapy - then resection	13.4%
		*

In a patient with symptomatic but unresectable *locally advanced rectal cancer*, who also has liver metastasis, what would your first treatment be:	Defunctioning stoma	95.6%
	Endoluminal stent if technically possible	4.4%
In a patient with asymptomatic and resectable *locally advanced rectal cancer*, and borderline operable liver metastasis, what would your first treatment be:	Induction chemotherapy (97%)	* 97%
	Short course radiotherapy, then systemic chemotherapy – then liver resection – then exenteration	3%
Chemotherapy for unresectable liver metastasis should entail:	FOLFOX/FOLFIRI + Biological depending on molecular testing	* 98.5%
	FolFox/FolFiri	1.5%
In setting of a patient that has oligometastatic disease and is deemed suitable for pelvic exenteration and liver resection, what is your preference	Stage Resection	74.8%
	Simultaneous Resection	25.2%
What is your opinion of one-stage resection of primary tumour (pelvic exenteration) and liver resection	Only in cases of limited hepatectomies	74.1%
	Only in favorable cases	13.1%
	Do not have the sub-specialties expertise available in same hospital to provide one-stage resection	12.6%
After R0 surgery of both rectal and liver tumour, would you consider adjuvant chemotherapy	Yes, routinely	* 85.9%
	Yes, in selected cases	14.1%
If for adjuvant chemotherapy, how long would you recommend	6-months	77.6%

	Depends	12.7%
	3-months	9.7%
How many liver metastases is it safe to remove in synchronous hepatic resection and pelvic exenteration	Depends on localization of lesions	66.7%
	Depends on liver remnant and resectability	22.1%
	Would not consider this as an option	11.1%

Table 1: Results from the final round of the *PelvEx Collaborative* Delphi Questionnaire. *Indicates consensus reached

SUPPORTING INFORMATION

PELVEX Collaborative:

Kelly ME, Aalbers AGJ, Abdul Aziz N, Abecasis N, Abraham-Nordling M, Akiyoshi T, Alberda W, Albert M, Andric M, Angenete E, Antoniou A, Auer R, Austin KK, Aziz O, Baker RP, Bali M, Baseckas G, Bebington B, Bednarski BK, Beets GL, Berg PL, Beynon J, Biondo S, Boyle K, Bordeianou L, Bremers AB, Brunner M, Buchwald P, Bui A, Burgess A, Burger JWA, Burling D, Campain N, Carvalhal S, Castro L, Caycedo-Marulanda A, Chan KKL, Chang GJ, Chew MH, C Chong P, Christensen HK, Clouston H, Codd M, Collins D, Colquhoun AJ, Corr A, Coscia M, Coyne PE, Creavin B, Croner RS, Damjanovic L, Daniels IR, Davies M, Davies RJ, Delaney CP, de Wilt JHW, Denost Q, Deutsch C, Dietz D, Domingo S, Dozois EJ, Duff M, Eglinton T, Enrique-Navascues JM, Espin-Basany E, Evans MD, Fearnhead NS, Flatmark K, Fleming F, Frizelle FA, Gallego MA, Garcia-Granero E, Garcia-Sabrido JL, Gentilini L, George ML, Ghouti L, Giner F, Ginther N, Glynn R, Golda T, Griffiths B, Harris DA, Hagemans JAW, Hanchanale V, Harji DP, Helewa RM, Heriot AG, Hochman D, Hohenberger W, Holm T, Hompes R, Jenkins JT, Kaffenberger S, Kandaswamy GV, Kapur S, Kanemitsu Y, Kelley SR, Keller DS, Khan MS, Kiran RP, Kim H, Kim HJ,

Koh CE, Kok NFM, Kokelaar R, Kontovounisios C, Kristensen HØ, Kroon HM, Kusters M, Lago V, Larsen SG, Larson DW, Law WL, Laurberg S, Lee PJ, Limbert M, Lydrup ML, Lyons A, Lynch AC, Mantyh C, Mathis KL, Margues CFS, Martling A, Meijerink WJHJ, Merkel S, Mehta AM, McArthur DR, McDermott FD, McGrath JS, Malde S, Mirnezami A, Monson JRT, Morton JR, Mullaney TG, Negoi I, Neto JWM, Nguyen B, Nielsen MB, Nieuwenhuijzen GAP, Nilsson PJ, O'Connell PR, O'Dwyer ST, Palmer G, Pappou E, Park J, Patsouras D, Pellino G, Peterson AC, Poggioli G, Proud D, Quinn M, Quyn A, Radwan RW, Rasheed S, Rasmussen PC, Regenbogen SE, Renehan A, Rocha R, Rochester M, Rohila J, Rothbarth J, Rottoli M, Roxburgh C, Rutten HJT, Ryan ÉJ, Safar B, Sagar PM, Sahai A, Saklani A, Sammour T, Sayyed R, Schizas AMP, Schwarzkopf E, Scripcariu V, Selvasekar C, Shaikh I, Shellawell G, Shida D, Simpson A, Smart NJ, Smart P, Smith JJ, Solbakken AM, Solomon MJ, Sørensen MM, Steele SR, Steffens D, Stitzenberg K, Stocchi L, Stylianides NA, Sumrien H, Sutton PA, Swartking T, Taylor C, Tekkis PP, Teras J, Thurairaja R, Toh EL, Tsarkov P, Tsukada Y, Tsukamoto S, Tuech JJ, Turner WH, Tuynman JB, van Ramshorst GH, van Zoggel D, Vasquez-Jimenez W, Verhoef C, Vizzielli G, Voogt ELK, Uehara K, Wakeman C, Warrier S, Wasmuth HH, Weber K, Weiser MR, Wheeler JMD, Wild J, Wilson M, Wolthuis A, Yano H, Yip B, Yip J, Yoo RN, Winter DC.