



A Seed in the Soil — Isolated Esophageal Cancer Recurrence in the Brain After Trimodality Treatment is more Common than Expected but Associated with Better Outcomes

Dana Ferrari-Light¹ · Robert E. Merritt¹ · Peter J. Kneuert¹

Accepted: 11 November 2022 / Published online: 18 November 2022

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Keywords Esophageal cancer · Brain metastases · Recurrence · Oligometastatic · Esophagectomy · Trimodality

Brain metastasis from esophageal carcinoma has historically been described as a rare phenomenon associated with a grave prognosis. However, therapeutic advances in multimodal treatments as well as improvements in the sensitivity of diagnostic imaging have led to an increase in the detection and treatment of metastatic brain disease in recent years. With great interest, we have read two related articles featured in the *Journal of Gastrointestinal Cancer* that detail recurrent brain metastases in surgically resected esophageal cancer patients and seek to further identify trends in diagnosis and treatment patterns that may stratify patients into better or worse prognosis [1, 2]. Both studies are interesting in that they demonstrate a higher-than-expected rate of esophageal cancer brain metastases in two different but contemporary patient populations — one from a clinical trial setting, and the other from an institutional experience. Both studies also highlight a short interval to recurrence in the brain within the first 12 months after surgery in most patients. For the clinician, these reports raise the questions of whether esophageal cancer recurrence in the brain is an under-recognized problem, and if actionable, whether it is worth screening some or all patients. We therefore sought to discuss these new studies in the context of the previous literature to develop an understanding of the incidence of esophageal cancer brain metastases after surgery, their predictability, and their treatment and outcomes (Table 1).

New Data on the Incidence of Brain Metastases

The first study by Smith et al. analyzed prospectively collected data on 85 patients combined from three phase II pre-operative chemoradiotherapy trials and showed that the brain was the first site of disease recurrence in 7% of patients after esophagectomy, with a median disease-free interval of only 5.4 months [1]. This study reports one of the highest rates of esophageal cancer recurrence in the brain to date, second only to a previous small phase II trial which found brain metastases in 10% of patients after trimodal therapy [3]. In comparison, a lower incidence of brain metastases is found in most surgical series, which may be related to less standardized surveillance protocols and varying neoadjuvant and adjuvant treatments (Table 1). The other study by Stuart et al. found recurrent disease isolated to the brain in 4.4% of patients at a median time of 8.4 months after surgery in their institutional cohort of patients that were almost all treated with neoadjuvant chemoradiation prior to minimally invasive esophagectomy [2]. Notably, their study found that the brain was the only site of recurrence in most patient with brain metastases, which confirms previous studies demonstrating that esophageal cancer recurrence after esophagectomy may be isolated to the brain in 60–78% of patients (Table 1) [2, 4, 5]. The detection of brain metastases in the study of Stuart et al. was based on new neurologic symptoms in all 15 patients [2]. Few other studies previously reported that symptoms were present in 66–83% of patients with brain metastases and preceded the diagnosis (Table 1) [3, 6]. Brain imaging is currently not recommended as part of the surveillance strategy, but may be warranted for patients with elevated risk, particularly within the 2 years of diagnosis based on the typical timeline of recurrent brain disease (Table 1).

However, our current understanding of which patients are at risk for brain metastases remains limited by the small

✉ Peter J. Kneuert
Peter.Kneuert@osumc.edu

¹ Thoracic Surgery Division, The Ohio State University
Wexner Medical Center, Doan Hall N846, 410 W 10Th Ave,
Columbus, OH 43210, USA

Table 1 Summary of studies on recurrent brain metastases in patients treated with trimodality therapy

Author	Publication year	Publication Data source	Total # of patients (N)	Preoperative chemo-RT	Incidence of brain mets	Subset of isolated brain metastases	Time to brain metastasis (median)	Factors associated with brain metastases	Neurologic symptoms	Survival after brain metastases detection (median)
Smith et al.*	2022	Phase II Clinical Trials	85	98%	6 (7%) first site	-	9.6 months	All adenocarcinoma	-	5.4 months
Stuart et al.*	2022	Institutional	339	95%	15 (4.4%) first site 9 (2.7%) isolated	60%	8.4 months	Primarily squamous cell	100%	14.3 months
Nobel et al	2021	Institutional	1760	61%	38 (2.2%) isolated	-	12 months	Diabetes, complete response	66%	12.0 months
Yoon et al	2016	Institutional	708	-	14 (2.0%) first site 11 (1.6%) isolated	78%	-	HER2 positive	-	5.9 months
Cleary et al	2016	Phase II Clinical Trial	40	100%	4 (10%) first site	-	13.9 months	Treatment response	83%	-
Wadhwa et al	2013	Institutional	518	100%	20 (3.9%) first site 12 (2.3%) isolated	60%	-	-	-	10.5 months

* New referenced studies

number of patients in most studies. Collectively, the current studies highlight that brain metastases may occur independent of the esophageal cancer histology. Specifically, Smith et al. noted that adenocarcinoma was the histology in all patients with first site of progression in the brain, while Stuart et al. found that isolated brain metastases occurred predominantly in squamous cell cancer patients [1, 2]. The largest study, which included 1760 patients after esophagectomy, showed that the histologic type did not impact the risk of brain metastases, and found that diabetes mellitus was the only independent risk factor associated with brain metastases [6]. The mechanism of this association is unclear. Complete pathologic treatment response was another factor that was strongly associated with isolated brain recurrence in this study [6]. The association of brain metastases with effective neoadjuvant chemoradiation treatments has also previously been noted by others [3, 7], and may be explained by the fact that neoadjuvant therapy can control esophageal cancer locoregionally and to some degree systemically, but may not reach circulating tumor cells beyond the blood–brain barrier. Furthermore, the overexpression of HER-2 may be a common pathway driving metastatic potential to the brain for esophageal cancer as previously recognized for breast cancer [3].

Treatment and Outcomes of Oligometastatic Brain Disease

Isolated brain metastases may be considered oligometastatic disease, a term that refers to an intermediate state of isolated metastatic disease at a favorable, predilected site before a later stepwise progression to other metastatic sites — known as the “seed and soil” hypothesis, first proposed in 1889 by Paget [8]. Metastatic esophageal cancer confined to one solid organ has been associated with a better prognosis as compared with widespread systemic recurrence [9]. Recent evidence showing that esophageal cancer metastases may respond well to local consolidative therapy further supports the concept of oligometastatic esophageal cancer, similar to what is known for oligometastatic lung, colorectal or breast cancer. A recent study by Krouse and colleagues showed that an aggressive approach to the treatment of oligometastatic esophagogastric cancer with local consolidative therapy by either metastasectomy or stereotactic radiation (SRS) in addition to systemic therapy was associated with a favorable prognosis when compared with systemic therapy alone (median survival 35 vs. 16 months, respectively) [10]. Specific to isolated brain metastases, the current study by Stuart and colleagues showed that most patients who recurred in the brain were amenable to surgery, SRS, or a combination of both. The survival rate in this cohort reached 44% at 2 years after the detection of brain disease recurrence [2]. Similarly

encouraging was the previous study by Nobel et al. who reported on the largest cohort of 38 patients with isolated brain recurrence of esophageal cancer, with a median survival of 12 months after their treatment for brain metastases that included surgery (79%) and/or whole brain radiation (71%), versus SRS (18%) [6].

Takeaways

Based on the new insights, we estimate that the current incidence of esophageal cancer brain metastases is higher than previously described, ranging between 4 and 7% after trimodality treatment. For most patients, the recurrence may be confined to the brain and amenable to surgery or stereotactic radiation. Specifically for patients with isolated recurrent brain disease, the prognosis after detection and treatment of brain metastases is also better than expected. The current studies highlight the importance of surveillance of neurologic symptoms and a low threshold for brain imaging for patients following trimodality therapy, particularly for those with a complete pathologic response and otherwise good prognosis.

Author Contribution The first draft of the manuscript was written by DFK and PK and all authors commented on previous versions of the manuscript. RM provided administrative support. All authors read and approved the final manuscript.

Data Availability The datasets generated during the current work are available from the corresponding author on reasonable request.

Declarations

Competing Interests None of the authors have any conflicts of interest to report. RM is a speaker for Intuitive Surgical.

References

- Smith RS, Foster NR, Jatoi A, Thome SD, Miller RC. Incidence of brain metastasis as first event in patients with esophageal carcinoma: a report from three prospective alliance clinical trials. *J Gastrointest Cancer*. 2022. Epub 2022/10/18. <https://doi.org/10.1007/s12029-022-00871-7>. PubMed PMID: 36251211.
- Stuart SK, Kuypers TJL, Martijnse IS, Heisterkamp J, Matthijsen RA. Patients with isolated brain metastases from esophageal carcinoma after minimally invasive esophagectomy may not have a dismal prognosis. *J Gastrointest Cancer*. 2022. Epub 2022/10/04. <https://doi.org/10.1007/s12029-022-00870-8>. PubMed PMID: 36192598.
- Cleary JM, Mamon HJ, Szymonifka J, Bueno R, Choi N, Donahue DM, Fidias PM, Gaissert HA, Jaklitsch MT, Kulke MH, Lynch TP, Mentzer SJ, Meyerhardt JA, Swanson RS, Wain J, Fuchs CS, Enzinger PC. Neoadjuvant irinotecan, cisplatin, and concurrent radiation therapy with celecoxib for patients with locally advanced esophageal cancer. *BMC Cancer*. 2016;16:468. Epub 2016/07/15. <https://doi.org/10.1186/s12885-016-2485-9>. PubMed PMID: 27412386; PMCID: PMC4944495.
- Yoon HH, Lewis MA, Foster NR, Sukov WR, Khan M, Sattler CA, Wiktor AE, Wu TT, Jenkins RB, Sinicrope FA. Central nervous system relapse in patients with untreated HER2-positive esophageal or gastroesophageal junction adenocarcinoma. *Int J Cancer*. 2016;139(7):1626–31. Epub 2016/05/21. <https://doi.org/10.1002/ijc.30200>. PubMed PMID: 27198655; PMCID: PMC6631306.
- Wadhwa R, Taketa T, Correa AM, Sudo K, Campagna MC, Blum MA, Komaki R, Skinner H, Lee JH, Bhutani MS, Weston B, Maru DM, Rice DC, Swisher S, Hofstetter WL, Ajani JA. Incidence of brain metastases after trimodality therapy in patients with esophageal or gastroesophageal cancer: implications for screening and surveillance. *Oncology*. 2013;85(4):204–7. Epub 2013/09/21. <https://doi.org/10.1159/000354736>. PubMed PMID: 24051869.
- Nobel TB, Dave N, Eljalby M, Xing X, Barbetta A, Hsu M, Tan KS, Janjigian Y, Bains MS, Sihag S, Jones DR, Molena D. Incidence and risk factors for isolated esophageal cancer recurrence to the brain. *Ann Thorac Surg*. 2020;109(2):329–36. Epub 2019/10/16. <https://doi.org/10.1016/j.athoracsur.2019.09.028>. PubMed PMID: 31614136; PMCID: PMC6982555.
- Rice TW, Khuntia D, Rybicki LA, Adelstein DJ, Vogelbaum MA, Mason DP, Murthy SC, Blackstone EH. Brain metastases from esophageal cancer: a phenomenon of adjuvant therapy? *Ann Thorac Surg*. 2006;82(6):2042–9. Epub 2006/11/28. <https://doi.org/10.1016/j.athoracsur.2006.06.089>. PubMed PMID: 17126108.
- Kroese TE, van Laarhoven HWM, Nilsson M, Lordick F, Guckenberger M, Ruurda JP, D'Ugo D, Haustermans K, van Cutsem E, van Hillegersberg R, van Rossum PSN. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: a systematic review and meta-analysis. *Eur J Cancer*. 2022;166:254–69. Epub 2022/03/28. <https://doi.org/10.1016/j.ejca.2022.02.018>. PubMed PMID: 35339868.
- Depypere L, Lerut T, Moons J, Coosemans W, Decker G, Van Veer H, De Leyn P, Naftoux P. Isolated local recurrence or solitary solid organ metastasis after esophagectomy for cancer is not the end of the road. *Dis Esophagus*. 2017;30(1):1–8. Epub 2016/10/06. <https://doi.org/10.1111/dote.12508>. PubMed PMID: 27704661.
- Kroese TE, Buijs GS, Burger MDL, Ruurda JP, Mook S, Broseus LAA, van Rossum PSN, van Hillegersberg R. Metastasectomy or stereotactic body radiation therapy with or without systemic therapy for oligometastatic esophagogastric cancer. *Ann Surg Oncol*. 2022;29(8):4848–57. Epub 2022/04/07. <https://doi.org/10.1245/s10434-022-11541-0>. PubMed PMID: 35381938; PMCID: PMC9246791.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.