Use of Circulating Tumor DNA in Prognostic Analysis of Patients with Solid Malignant Tumors of the Gastrointestinal Tract: Systematic Review

https://doi.org/10.32635/2176-9745.RBC.2024v70n4.4873

Utilização de DNA Tumoral Circulante na Análise de Prognóstico de Pacientes com Tumores Malignos Sólidos do Trato Gastrintestinal: Revisão Sistemática

Uso del ADN Circulante Tumoral en el Análisis pronóstico de Pacientes con Tumores Malignos Sólidos del Tracto Gastrointestinal: Revisión Sistemática

Gabriel dos Santos Martins de Abreu[1]; Mariana Albuquerque de Brito[2]; Ana Paula de Souza Ramos[3]

ABSTRACT

Introduction: The circulating tumor DNA (ctDNA), one of the main exponents of liquid biopsy, constitutes a promising tool in the field of oncology. However, its use in clinical practice, despite being varied, requires further support. **Objective:** To evaluate the impact of using ctDNA as a tool to qualify the prognosis of patients with solid malignant tumors of the gastrointestinal tract. **Method:** Systematic review based on cohort studies, using the MEDLINE, LILACS, SciELO, Science Direct and BASE databases. The assessment of methodological quality was carried out by the Newcastle-Ottawa Quality Assessment Scale. **Results:** Of the 557 articles initially found, the final sample of the present study included 13 articles. Higher rates of tumor recurrence and lower survival rates were observed in ctDNA-positive patients with tumors from all main sites of the gastrointestinal tract, compared to those who were ctDNA-negative. This correlation was consistent across all tumor stages. Furthermore, ctDNA proved to be more effective in predicting tumor recurrence proven by radiological examination when compared to carcinoembryonic antigen, typically used in this context. **Conclusion:** The results found support the use of ctDNA in the described scenario, in a complementary way to the prognostic assessment tools commonly used in current clinical practice.
Keywords: Liquid biopsy/methods; Circulating Tumor DNA; Prognosis; Gastrointestinal Tract/pathology.

RESUMO

Introdução: O DNA tumoral circulante (ctDNA), um dos principais expoentes da biópsia líquida, constitui uma ferramenta promissora na área da oncologia. Contudo, seu uso na prática clínica, apesar de variado, necessita de maiores embasamentos. **Objetivo:** Avaliar o impacto da utilização do ctDNA como ferramenta para qualificar o prognóstico de pacientes com tumores malignos sólidos do trato gastrintestinal. **Método:** Revisão sistemática baseada em estudos do tipo coorte, utilizando as bases de dados MEDLINE, LILACS, SciELO, *Science Direct* e BASE. A avaliação da qualidade metodológica foi feita pela *Newcaslte-Ottawa Quality Assessment Scale*. **Resultados:** Dos 557 artigos encontrados inicialmente, a amostra final do presente estudo contou com 13 artigos. Observaram-se maiores taxas de recidiva tumoral e menores taxas de sobrevida em pacientes ctDNA-positivos com tumores de todos os principais sítios do trato gastrintestinal, em relação àqueles ctDNA-negativos. Essa correlação foi consistente ao longo de todos os estádios tumorais. Ademais, o ctDNA se mostrou mais eficaz na predição de recidiva tumoral comprovada por exame radiológico quando comparado ao antígeno carcinoembrionário, tipicamente utilizado nesse contexto. **Conclusão:** Os resultados encontrados apoiam a utilização do ctDNA no cenário descrito, de modo complementar às ferramentas de avaliação de prognóstico comumente utilizadas na prática clínica atual.
Palavras-chave: Biópsia líquida/métodos; DNA Tumoral Circulante; Prognóstico; Trato gastrintestinal/patologia.

RESUMEN

Introducción: El ADN circulante tumoral (ADNct), uno de los principales exponentes de la biopsia líquida, constituye una herramienta prometedora en el campo de la oncología. Sin embargo, su uso en la práctica clínica, a pesar de ser variado, requiere mayor sustento. **Objetivo:** Evaluar el impacto del uso del ADNct como herramienta para calificar el pronóstico de pacientes con tumores sólidos malignos del tracto gastrointestinal. **Método:** Revisión sistemática basada en estudios de cohortes, utilizando las bases de datos MEDLINE, LILACS, SciELO, *Science Direct* y BASE. La evaluación de la calidad metodológica se realizó mediante la *Newcastle-Ottawa Quality Assessment Scale*. **Resultados:** De los 557 artículos encontrados inicialmente, la muestra final del presente estudio incluyó 13 artículos. Se observaron tasas más altas de recurrencia tumoral y tasas de supervivencia más bajas en pacientes con ADNct positivo con tumores de todos los sitios principales del tracto gastrointestinal, en comparación con aquellos con ADNct negativo. Esta correlación fue consistente en todas las etapas del tumor. Además, el ADNct demostró ser más eficaz para predecir la recurrencia del tumor verificada mediante examen radiológico en comparación con el antígeno carcinoembrionario, típicamente utilizado en este contexto. **Conclusión:** Los resultados encontrados apoyan el uso de ADNct en el escenario descrito, de forma complementaria a las herramientas de evaluación pronóstica habitualmente utilizadas en la práctica clínica actual.
Palabras clave: Biopsia líquida/métodos; ADN Circulante Tumoral; Pronóstico; Tracto Gastrointestinal/patología.

[1-3]Universidade Estadual do Sudoeste da Bahia (Uesb). Jequié (BA), Brasil.
[1]E-mail: gabrielsmabreu@gmail.com. Orcid iD: https://orcid.org/0009-0000-4270-2519
[2]E-mail: marianaalbuquerquebrito50@gmail.com. Orcid iD: https://orcid.org/0000-0002-4101-464X
[3]E-mail: aninharamos.bio@gmail.com. Orcid iD: https://orcid.org/0000-0002-5805-9596
Corresponding author: Gabriel dos Santos Martins de Abreu. Av. José Moreira Sobrinho, S/N – Jequiezinho. Jequié (BA), Brasil. CEP 45205-490. E-mail: gabrielsmabreu@gmail.com

INTRODUCTION

In 2022, about 20 million cancer cases and 9.7 million deaths caused by the disease were recorded globally[1]. In Brazil, there is a similar scenario, with more than 16% of deaths occurring due to malignant tumors[2].

This epidemiological scenario can be partially explained by the broad exposure of the population to risk factors determining the emergence of diseases, such as chemical, physical, and biological agents with carcinogenic potential. In addition, the gradual reversal of the age pyramid, resulting from continuous improvements in the health, pharmacology, and infrastructure sectors, has provided an increasing life expectancy. Although this phenomenon is essentially positive, advanced age is known to be one of the main risk factors for several types of cancer[2].

Therefore, while the field of oncology has grown significantly in recent decades, there is a growing need for understanding the physiopathological processes that lead to malignancy, as well as different forms of screening, diagnosis, prognosis assessment, and treatment of the disease. In this scenario, biomarkers arise as a powerful tool for evaluating the oncological patient, being able to circumvent some of the greatest difficulties of the main methods still used, such as traditional biopsies[3].

In the biomarker spectrum, liquid biopsy has gained prominence because of its promising potential in the evaluation of cancer patients in all the aforementioned steps. This non-invasive technique allows not only the analysis of circulating tumor cells (CTC) but also the evaluation of circulating tumor DNA (ctDNA). CtDNA represents one of the main strands of this procedure, able to correlate the activity of the disease with the levels of DNA molecules derived from tumor cells present in the blood circulation, due to a variety of biochemical mechanisms[4].

The use of ctDNA as an oncological evaluation tool is particularly useful in cases of gastrointestinal tract tumors (GIT). In addition to the high epidemiological relevance, manifested by high incidence and mortality rates in Brazil and worldwide, GIT tumors are difficult to detect early, due to their scarce and unspecific symptomatology in their early stages[5].

It is important to highlight that the accuracy of this correlation is not uniform between distinct types of tumors and in the various phases of oncological evaluation. Therefore, the need to conduct additional studies in order to clarify the most effective applications of this technology becomes evident. The objective of this study is to evaluate the impact of the use of ctDNA as a tool to qualify the prognosis of patients with solid malignant tumors of the gastrointestinal tract.

METHOD

Systematic literature review, whose writing basis was the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol (PRISMA)[6]. This systematic review was recorded in the International PROSPECTIVE Register of Systematic Reviews (PROSPERO)[7] database, identified by number CRD42023460611.

Because it is a prognostic study, the strategy adopted was based on the PECO acronym, which consists of the initials Population, Exposure, Comparison, and Outcome, with the following research question: What is the benefit of using ctDNA as a tool to qualify the prognosis of patients with solid malignant tumors of the gastrointestinal tract?

This review used the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (SciELO), and Science Direct, in addition to the Bielefeld Academic Search Engine.

The descriptors used to search for scientific articles in this study consisted of the controlled terms of the Medical Subject Headings (MeSH): "circulating tumor dna", "liquid biopsy", "prognosis", "gastrointestinal cancer", "esophageal cancer", "gastric cancer", "intestinal cancer" and "rectal cancer". Their alternative terms were also searched. The Boolean operator "OR" was used between the controlled terms and their alternative terms, while the "AND" operator was used among the components of the PECO acronym explained earlier, being this strategy applied in the advanced search fields in each database. There was no restriction on the year of publication, language, or geographic location.

This study included case-control and cohort-type articles that evaluated the effectiveness of the measurement of ctDNA values in determining the prognosis of patients with solid malignant tumors of the gastrointestinal tract (esophageal, stomach, intestines, and rectum cancers), without distinction of age or sex.

Qualitative research, as well as other types of literature review, were excluded, in addition to articles in which ctDNA levels were related to metastatic processes or neoplasms of GIT accessory glands. Two independent researchers conducted the selection of studies. In case of disagreement between them regarding the inclusion or exclusion of articles, a third reviewer intervened.

After the database search, the retrieved works were allocated to the Rayyan application, whose purpose is to assist in the construction of systematic reviews with

meta-analysis[8]. After deleting duplicate works, a reading of titles and abstracts was conducted initially, followed by the evaluation of the full text. The studies were blindly selected following the aforementioned strategy. All those steps were conducted independently.

The data extraction, compiled in a Microsoft Excel spreadsheet, was also blindly performed by two independent researchers. The data obtained were authors, year of publication, journal name, country, objective, study design, location and period of collection, sample size and control, prognostic tools, and main results.

The assessment of the methodological quality of the articles was conducted according to the Newcastle-Ottawa criteria. This assessment was made by two authors independently for each of the studies. For presenting the results, a synthesis of the qualitative data of included studies was elaborated using charts and tables.

RESULTS

The initial search in the databases found 557 articles, of which 555 remained after the removal of duplicates. Another 454 studies were excluded after reading the title and abstract. Of the 101 articles read in full, eight met the eligibility criteria. In addition, five new articles were incorporated into the final review, identified by analyzing the relevant references from the reviews leveraged in the initial research, composing a final sample of 13 articles included in this review. The process is illustrated in the flowchart proposed by the PRISMA protocol (Figure 1), in which the description of the results of the search and selection process is assumed, including number of studies identified in the initial search up to the number of studies included in the review[9].

Most of the selected studies were carried out in China (30%), followed by Australia (23%), the United

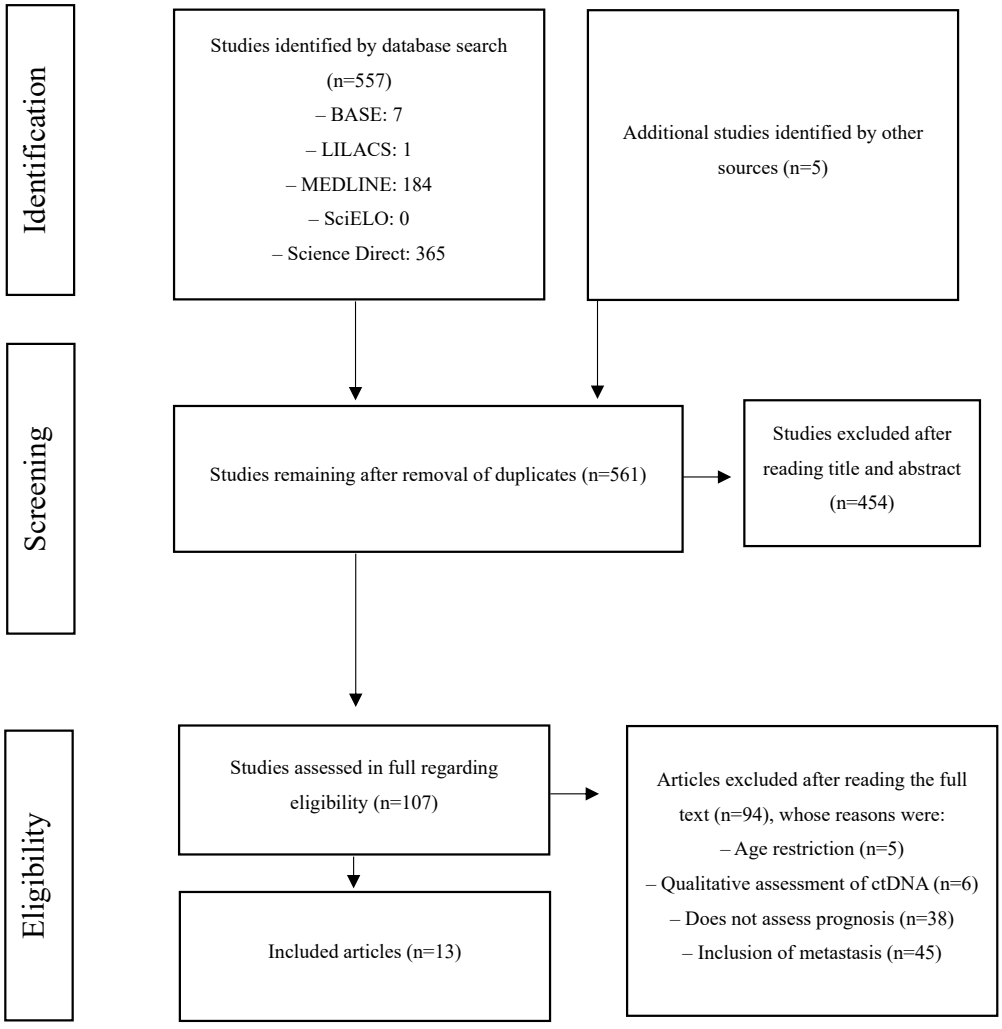

Figure 1. PRISMA flowchart
Caption: ctDNA = circulating tumor DNA.

States (15%) and Denmark (15%), and published in the years 2022, 2021 and 2019 (69%), with the most recent published in 2023 (7.6%) and the oldest in 2016 (7.6%). The sample size of the studies varied from 29 to 295 participants. Colorectal cancer (84.6%), followed by gastric cancer (15%), was the most frequently approached neoplasm. Only one study analyzed esophageal cancer (7.6%). The general characteristics of the studies are identified in Chart 1[10-22].

Regarding prognostic tools, all 13 articles (100%) used at least one tool in addition to ctDNA evaluation, the main ones being carcinoembryonic antigen (CEA), present in nine studies (69%)[10-18], and computed tomography (CT), present in all 13 studies (100)[10-22]. This information can be viewed in Chart 2[10-22].

Regarding gastroesophageal tumors, a significantly higher recurrence rate was found in ctDNA-positive patients in relation to ctDNA-negative patients in the context of the minimal residual disease (MRD) window (within 16 weeks after tumor resection surgery before the onset of adjuvant therapy)[19], as well as a worse three-year survival in patients with detectable ctDNA, both in the post-surgical context and after neoadjuvant therapy. Patients who were initially ctDNA-negative and became ctDNA-positive after neoadjuvant therapy presented worse overall survival[20].

The same trend was observed in cases of colon cancer, in which ctDNA positivity was related to worse survival in three years, compared to the negativity of the biomarker[15,21]. Li et al.[21] proposed a new form of risk stratification in patients with colon neoplasms based on the inclusion of ctDNA to the other previously used factors, finding an effective correlation between risk levels and tumor recurrence.

Additionally, CEA was less present than ctDNA at the time of recurrence in patients with colon tumors in stage II, with a significantly greater interval between ctDNA elevation and radiological evidence of tumor recurrence compared to CEA elevation time[14].

In studies that evaluated colorectal cancer, a higher ctDNA positivity was found consistently in tumors at stages II and III compared to those at stage I. However, in general, detectable levels of ctDNA in these patients were associated with worse recurrence rates in at least two years[10,13]. In addition, a minimal risk of tumor recurrence was found for ctDNA-negative patients, regardless of whether they had undergone adjuvant therapy or not[13]. In this context, the possible advantage of the use of ctDNA in the prediction of relapses before its radiological proof is highlighted in comparison to CEA[13,17].

Regarding rectal cancers, the detection of ctDNA was also associated with the worst overall survival in three years, both in the postoperative scenario and even before the onset of neoadjuvant therapy[16,22]. In addition, the resection rate R0 (macroscopically complete resection with histologically negative margins) was significantly higher among patients with undetectable preoperative ctDNA compared to those ctDNA-positive[12].

The evaluation of methodological quality according to the Newcastle- Ottawa Quality Assessment Scale showed that the mean score of the studies was 8.69 (standard deviation: ± 0.87). Among the studies, 11 (84%) obtained maximum

Chart 1. General characteristics of the studies included

Author	Year	Collection period	Country	Study design	Sample size	Type of tumor
Chen et al.[10]	2021	Sep 2017 – Mar 2020	China	Cohort	276	Colorectal
Henriksen et al.[11]	2022	Jul 2014 – Feb 2019	Denmark	Cohort	168	Colorectal
McDuff et al.[12]	2021	Jan 2014 – Feb 2018	USA	Cohort	29	Colorectal
Reinert et al.[13]	2019	May 2014 – Jan 2017	Denmark	Cohort	130	Colorectal
Tie et al.[14]	2016	Jul 2011 – Sep 2014	Australia	Cohort	250	Colorectal
Tie et al.[15]	2019	Nov 2014 – May 2017	Australia	Cohort	100	Colorectal
Tie et al.[16]	2019	Apr 2012 – Dec 2015	Australia	Cohort	200	Colorectal
Wang et al.[17]	2019	Feb 2007 – May 2013	Sweden	Cohort	63	Colorectal
Zhou et al.[18]	2021	Aug 2017 – Feb 2019	China	Cohort	106	Colorectal
Huffman et al.[19]	2022	Sep 2019 – Feb 2022	USA	Cohort	295	Esophageal and gastric
Zhang et al.[20]	2023	Nov 2017 – Jan 2020	China	Cohort	79	Gastric
Li et al.[21]	2022	Aug 2018 – Dec 2019	China	Cohort	165	Colorectal
Pazdirek et al.[22]	2020	2013– 2017	Czech Republic	Cohort	36	Colorectal

Chart 2. Prognostic tools and main results of the included studies

Author	Year	Prognostic tools	Main Results
Chen et al.[10]	2021	ctDNA, CEA, CT	In the preoperative period, ctDNA was detectable in 64.2% of the patients; in the postoperative period, ctDNA negativity was associated with a recurrence-free survival rate of 89.4% in contrast to 39.9% of the ctDNA-positive patients. The ctDNA samples were collected in the preoperative, postoperative periods and six months after surgery serially every three months until month 24, or patient's withdrawal from the study, or death, and were analyzed using next-generation sequencing
Henriksen et al.[11]	2022	ctDNA, CEA, CT	There was a recurrence rate of 80% in the ctDNA-positive patients in the postoperative period and, in this context, ctDNA exceeded the ≥ 70 age, T4, degree of tumor differentiation, and CEA as a predictor of recurrence-free survival; after adjuvant therapy, 100% of the patients who were not ctDNA-negative in the follow-up period experienced recurrence. The ctDNA samples were collected during the diagnosis, in the postoperative period, during adjuvant therapy and after its completion, and in routine follow-ups, every three months for up to three years, analyzed using next-generation sequencing
McDuff et al.[12]	2021	ctDNA, CEA, CT	Resection rate R0 (macroscopically complete resection with histologically negative margins) was significantly higher among patients with undetectable preoperative ctDNA (88%) compared to those ctDNA-positive (44%). The ctDNA samples were collected, in a unique way, in the preoperative and postoperative periods, and analyzed using next-generation sequencing
Reinert et al.[13]	2019	ctDNA, CEA, CT	The detection of ctDNA in stages II and III tumors was significantly higher than those in stage I; the mean time of detection of high ctDNA levels in patients who completed the definitive treatment until the evidence of recurrence through CT was 8.7 months. The ctDNA samples were collected before and after the surgical intervention, analyzed through next-generation sequencing, and serialized every three months until death, patient withdrawal from the study, or month 36
Tie et al.[14]	2016	ctDNA, CEA, CT	Radiological recurrence was detected in 78.6% of ctDNA-positive patients not treated with adjuvant therapy; in the follow-up period, ctDNA was more often positive than CEA at the time of recurrence, besides presenting elevation in its levels at a significantly longer time than CEA until the radiological evidence of tumor recurrence. The ctDNA samples were collected after surgical intervention, analyzed by a safe-sequencing system, and serialized every three months for up to two years
Tie et al.[15]	2019	ctDNA, CEA, CT	Recurrence-free survival in three years was 33% for ctDNA-positive postoperative patients and 87% for ctDNA-negative patients; a similar pattern was also found after neoadjuvant therapy (50% and 85%, respectively). The ctDNA samples were collected uniquely, before and after the beginning of the pre-treatment (radiochemotherapy), and 4-10 weeks after surgical intervention, and were analyzed by a safe-sequencing system

Continue...

Chart 2. Continuation.

Author	Year	Prognostic tools	Main Results
Tie et al.[16]	2019	ctDNA, CEA, CT	After surgery, three-year survival in ctDNA-positive patients was 47%; the post-surgical status of ctDNA had the strongest independent association with the recurrence-free interval. The ctDNA samples were collected uniquely after surgical intervention and at the end of the treatment, analyzed by a safe-sequencing system
Wang et al.[17]	2019	ctDNA, CEA, CT	In the postoperative period, there was a positivity of ctDNA between 2 and 31 months before the radiological evidence of tumor recurrence; 100% of the patients who had recurrence presented ctDNA detectable in the follow-up period. The ctDNA samples were collected one month after surgical intervention, serialized every three to six months, and analyzed using a safe-sequencing system
Zhou et al.[18]	2021	ctDNA, CEA, CA19-9, CT	The detection of ctDNA in the baseline was positively correlated with the occurrence of distant metastases in a shorter period than those patients whose ctDNA was undetectable. This correlation was positive at all times of dosage. CtDNA samples were collected serially in the baseline, during neoadjuvant radiochemotherapy, in the preoperative and postoperative period, and were analyzed using next-generation sequencing
Huffman et al.[19]	2022	ctDNA, CT	CtDNA was present in about one-fifth of the patients in the postoperative setting, associated with a recurrence rate of 81.2%; in all analyzed scenarios, there was a similarity of results in the various tumor subtypes. The ctDNA samples were collected in the preoperative, postoperative, and serially during routine clinical follow-up at medical criteria, and were analyzed using next-generation sequencing
Zhang et al.[20]	2023	ctDNA, CT	The three-year survival estimate for ctDNA-negative and ctDNA-positive patients was 73% and 34%, respectively, after neoadjuvant therapy and 68% and 38%, respectively, after surgery. The ctDNA samples were collected uniquely before neoadjuvant chemotherapy, after neoadjuvant chemotherapy, and after surgery, analyzed through next-generation sequencing
Li et al.[21]	2022	ctDNA, CT	Recurrence-free survival in ctDNA-positive patients after adjuvant chemotherapy was 45.5%, in contrast to 72.7% of ctDNA-negative patients. The ctDNA samples were collected before and after chemotherapy in non-serial mode, analyzed through next-generation sequencing
Pazdirek et al.[22]	2020	ctDNA, CT	The overall survival rate in patients whose ctDNA was negative was 91.2%. The subgroup rate of patients whose ctDNA was positive corresponded to 71.4%. CtDNA samples were collected serially before therapy and at the end of the first week. The technologies used for analysis were denaturant capillary electrophoresis and BEAMING assay

Captions: ctDNA = circulating tumor DNA, CEA = carcinoembryonic antigen, CA19-9 = carbohydrate antigen 19-9, CT = computed tomography.

score, one study (7.6%) added eight points, and another study (7.6%) obtained six points, as verified in Chart 3.

DISCUSSION

Faced with the challenge of accurately determining the prognosis of the oncological patient, recent technologies have emerged to more effectively guide the treatment of malignant neoplasms. Among them, liquid biopsy has gained prominence in recent years, predominantly represented by ctDNA. Although its applicability in clinical practice is still relatively restricted – due to its high cost and low availability, especially in developing countries – several studies discuss its promising character

Chart 3. Evaluation of methodological quality using the Newcastle-Ottawa Quality Assessment Scale

Author	Year	Selection	Comparability	Outcome	Total
Chen et al.[10]	2021	++++	++	+++	9/9
Henriksen et al.[11]	2022	++++	++	+++	9/9
McDuff et al.[12]	2021	++	++	++	6/9
Reinert et al.[13]	2019	++++	++	+++	9/9
Tie et al.[14]	2016	++++	++	+++	9/9
Tie et al.[15]	2019	++++	++	+++	9/9
Tie et al.[16]	2019	++++	++	+++	9/9
Wang et al.[17]	2019	++++	++	+++	9/9
Zhou et al.[18]	2021	++++	++	+++	9/9
Huffman et al.[19]	2022	++++	++	+++	9/9
Zhang et al.[20]	2023	++++	++	++	8/9
Li et al.[21]	2022	++++	++	+++	9/9
Pazdirek et al.[22]	2020	++++	++	+++	9/9

in the evaluation of prognosis and risk stratification, with the possibility of identifying patients with MRD and guiding the need for adjuvant therapy, as well as verifying its effectiveness[23,24].

The articles analyzed in this review found a positive correlation between the detection of ctDNA and unfavorable prognoses in patients with solid malignant tumors of the gastrointestinal tract, compared to those ctDNA-negative. In the case of gastroesophageal tumors, not only was tumor recurrence higher in ctDNA-positive patients but there was also worse survival in three years. In colorectal tumors, the same trend was observed: there was worse survival in three years and worse recurrence rates, as well as a greater space between the elevation of ctDNA levels and the radiological proof of recurrence compared to the verification of CEA levels for the same purpose.

Jiang et al.[25], when conducting a literature review on the prognosis of esophageal cancer, found that ctDNA detectable after treatment at any time point was correlated with a worse prognosis in general, which corroborates the results obtained in this study. Similarly, Gao et al.[26], when carrying out a systematic review with meta-analysis that discussed gastric cancer, pointed out that ctDNA detection was also associated with worse recurrence-free survival rates and overall survival rates. Although only four articles could have been evaluated for this last parameter, the study used a similar methodology to that of the present study, which reinforces the findings described.

As for colorectal cancer, another systematic review of the literature states that the positivity of ctDNA correlated in the same way with the rates previously mentioned. It is noteworthy that the study focused on some of the genetic and epigenetic mutations found in ctDNA and how these could relate to the patient's prognosis, reporting that there was a slight level of heterogeneity of this evaluation in its results[27].

The next-generation sequencing (NGS) ctDNA analysis performed with the aid of a genetic panel, for example, can identify known variations in the genes of some tumors[28]. By detecting some of these alterations, liquid biopsy allows a qualitative evaluation of ctDNA, correlating specific genetic alterations to more or less favorable prognostics[29].

Chen et al.[30], in their systematic review with meta-analysis, observed that ctDNA positivity was an important indicator of colorectal tumor recurrence, a pattern observed in all studies analyzed, which did not change with time and place of the study, and which showed greater effectiveness in evaluating the prognosis of tumors at stages I to III. It is worth noting that five of the articles included in this meta-analysis were also included in the scope of this study, thus reinforcing the convergence of the results obtained.

Monitoring during oncological treatments may reveal an important reduction in ctDNA levels after initial intervention, showing an adequate clinical response[31]. On the other hand, the subsequent elevation of ctDNA during longitudinal follow-up is a possible indication of MRD and consequent therapeutic failure[32].

In addition, a study published in 2019, whose objectives include the evaluation of ctDNA as a tool for prognostic evaluation in patients with rectal tumors, found a similar correlation between the persistence of

ctDNA after treatment and tumor recurrence in the follow-up period in the vast majority of the articles included in its review[33].

Regarding its limitations, the present study deals with problems related to the very nature of ctDNA evaluation. Currently, there is still no consensus on the most effective way to obtain this biomarker, so there is, in the literature, a great heterogeneity of technologies such as NGS, digital PCR (dPCR), and cancer-customized profiling by deep sequencing (CAPP-Seq), all capable of performing this analysis[23]. Also, there is no exact regularity regarding the time of collection of ctDNA within the context of neoadjuvant therapy, surgery, and adjuvant therapy, inconsistencies which are naturally found throughout the studies addressed.

CONCLUSION

CtDNA, one of the main exponents of liquid biopsy, shows signs of success in evaluating the prognosis of patients with solid malignant tumors of the gastrointestinal tract. The results found in this study suggest that there is, in recent literature, evidence to support its applicability in clinical practice in the specific scenario described, especially in a complementary way to the most used prognostic evaluation tools.

Further studies may seek greater standardization in the way ctDNA is collected and evaluated, given the different possibilities that are currently available. Moreover, the realization of multi-centric studies, capable of testing the applicability of ctDNA in regions where the practice has been less explored – such as Latin America – can provide more subsidy for the application of this tool in the clinical area, by verifying the probable persistence of its potential in scenarios in which population characteristics are distinct.

CONTRIBUTIONS

Gabriel dos Santos Martins de Abreu and Mariana Albuquerque de Brito have substantially contributed to the study design, acquisition, analysis, and data interpretation, wording, and critical review. Ana Paula de Souza Ramos has substantially contributed to the study design, data acquisition, analysis, and interpretation, wording, and critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

FUNDING SOURCES

None.

REFERENCES

1. American Cancer Society. Global cancer facts & figures. 5 ed. Nova Yorke: ACS; 2024.
2. Souza T, Migowski A, Ribeiro C, et al. ABC do câncer: abordagens básicas para o controle do câncer. 6 ed rev atual. Rio de Janeiro: INCA; 2020.
3. Vaidyanathan R, Soon RH, Zhang P, et al. Cancer diagnosis: from tumor to liquid biopsy and beyond. Lab Chip. 2019;19:11-34. doi: https://doi.org/10.1039/c8lc00684a
4. Pessoa LS, Heringer M, Ferrer VP. ctDNA as a cancer biomarker: a broad overview. Crit Rev Oncol Hematol. 2020;155:103109. doi: https://doi.org/10.1016/j.critrevonc.2020.103109
5. Leso H, Moraes J, Amorim I, et al. Epidemiologia do câncer do trato gastrointestinal em itumbiara, Goiás, entre 1999 e 2019. RSD. 2022;11(15). doi: https://doi.org/10.33448/rsd-v11i15.37540
6. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647. doi: https://doi.org/10.1136/bmj.g7647
7. University of York. Centre for Reviews and Dissemination. New York: University of York; 2019. PROSPERO - International prospective register of systematic reviews. 2023. [acesso 2023 ago 31]. Disponível em: https://www.crd.york.ac.uk/PROSPERO/
8. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. doi: https://doi.org/10.1186/s13643-016-0384-4
9. Page MJ, McKenzie JE, Bossuyt PM, et al. A declaração PRISMA 2020: diretriz atualizada para relatar revisões sistemáticas. Epidemiol Serv Saúde. 2022;31(2):e2022107. doi: http://dx.doi.org/10.1590/s1679-49742022000200033
10. Chen G, Peng J, Xiao Q, et al. Postoperative circulating tumor DNA as markers of recurrence risk in stages II to III colorectal cancer. J Hematol Oncol. 2021;14(1):80. doi: https://doi.org/10.1186/s13045-021-01089-z
11. Henriksen TV, Tarazona N, Frydendahl A, et al. Circulating tumor DNA in stage III colorectal cancer, beyond minimal residual disease detection, toward assessment of adjuvant therapy efficacy and clinical behavior of recurrences. Clin Cancer Res. 2022;28(3):507-17. doi: https://doi.org/10.1158/1078-0432.ccr-21-2404

12. McDuff SGR, Hardiman KM, Ulintz PJ, et al. Circulating tumor DNA predicts pathologic and clinical outcomes following neoadjuvant chemoradiation and surgery for patients with locally advanced rectal cancer. JCO Precis Oncol. 2021;5:PO.20.00220. doi: https://doi.org/10.1200/po.20.00220
13. Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. JAMA Oncol. 2019;5(8):1124-31. doi: https://doi.org/10.1001/jamaoncol.2019.0528
14. Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med. 2016;8(346):346ra92. doi: https://doi.org/10.1126/scitranslmed.aaf6219
15. Tie J, Cohen JD, Wang Y, et al. Circulating tumor DNA analyses as markers of recurrence risk and benefit of adjuvant therapy for stage III colon cancer. JAMA Oncol. 2019;5(12):1710-7. doi: https://doi.org/10.1001/jamaoncol.2019.3616
16. Tie J, Cohen JD, Wang Y, et al. Serial circulating tumour DNA analysis during multimodality treatment of locally advanced rectal cancer: a prospective biomarker study. Gut. 2019;68(4):663-71. doi: https://doi.org/10.1136/gutjnl-2017-315852
17. Wang Y, Li L, Cohen JD, et al. Prognostic potential of circulating tumor DNA measurement in postoperative surveillance of nonmetastatic colorectal cancer. JAMA Oncol. 2019;5(8):1118-23. doi: https://doi.org/10.1001/jamaoncol.2019.0512
18. Zhou J, Wang C, Lin G, et al. Serial circulating tumor DNA in predicting and monitoring the effect of neoadjuvant chemoradiotherapy in patients with rectal cancer: a prospective multicenter study. Clin Cancer Res. 2021;27(1):301-10. doi: https://doi.org/10.1158/1078-0432.ccr-20-2299
19. Huffman BM, Aushev VN, Budde GL, et al. Analysis of circulating tumor DNA to predict risk of recurrence in patients with esophageal and gastric cancers. JCO Precis Oncol. 2022;(6):e2200420. doi: https://doi.org/10.1200/po.22.00420
20. Zhang M, Yang H, Fu T, et al. Liquid biopsy: circulating tumor DNA monitors neoadjuvant chemotherapy response and prognosis in stage II/III gastric cancer. Mol Oncol. 2023;17(9):1930-42. doi: https://doi.org/10.1002/1878-0261.13481
21. Li Y, Mo S, Zhang L, et al. Postoperative circulating tumor DNA combined with consensus molecular subtypes can better predict outcomes in stage III colon cancers: a prospective cohort study. Eur J Cancer. 2022;169:198-209. doi: https://doi.org/10.1016/j.ejca.2022.04.010
22. Pazdirek F, Minarik M, Benesova L, et al. Monitoring of early changes of circulating tumor dna in the plasma of rectal cancer patients receiving neoadjuvant concomitant chemoradiotherapy: evaluation for prognosis and prediction of therapeutic response. Front Oncol. 2020;10:1028. doi: https://doi.org/10.3389/fonc.2020.01028
23. Peng Y, Mei W, Ma K, et al. Circulating tumor DNA and minimal residual disease (MRD) in solid tumors: current horizons and future perspectives. Front Oncol. 2021;11:763790. doi: https://doi.org/10.3389/fonc.2021.763790
24. Ueberroth BE, Jones JC, Bekaii-Saab TS. Circulating tumor DNA (ctDNA) to evaluate minimal residual disease (MRD), treatment response, and posttreatment prognosis in pancreatic adenocarcinoma. Pancreatology. 2022;22(6):741-8. doi: https://doi.org/10.1016/j.pan.2022.06.009
25. Jiang M, Zhou H, Jiang S, et al. A review of circulating tumor DNA in the diagnosis and monitoring of esophageal cancer. Med Sci Monit. 2022;28:e934106. doi: https://doi.org/10.12659/msm.934106
26. Gao Y, Zhang K, Xi H, et al. Diagnostic and prognostic value of circulating tumor DNA in gastric cancer: a meta-analysis. Oncotarget. 2016;8(4):6330-40. doi: https://doi.org/10.18632/oncotarget.14064
27. Fan G, Zhang K, Yang X, et al. Prognostic value of circulating tumor DNA in patients with colon cancer: systematic review. PLoS One. 2017;12(2):e0171991. doi: https://doi.org/10.1371/journal.pone.0171991
28. Cimmino F, Lasorsa VA, Vetrella S, et al. A targeted gene panel for circulating tumor DNA sequencing in neuroblastoma. Front Oncol. 2020;10:596191. doi: https://doi.org/10.3389/fonc.2020.596191
29. Lim Y, Kim S, Kang JK, et al. Circulating tumor DNA sequencing in colorectal cancer patients treated with first-line chemotherapy with anti-EGFR. Sci Rep. 2021;11:16333. doi: https://doi.org/10.1038/s41598-021-95345-4
30. Chen Y, Mo S, Wu M, et al. Circulating tumor DNA as a prognostic indicator of colorectal cancer recurrence - a systematic review and meta-analysis. Int J Colorectal Dis. 2022;37(5):1021-7. doi: https://doi.org/10.1007/s00384-022-04144-4
31. Cheng ML, Lau CJ, Milan MSD, et al. Plasma ctDNA response is an early marker of treatment effect in advanced NSCLC. JCO Precis Oncol. 2021;5:PO.20.00419. doi: https://doi.org/10.1200/po.20.00419

32. Sharbatoghli M, Vafaei S, Aboulkheyr ESH, et al. Prediction of the treatment response in ovarian cancer: a ctDNA approach. J Ovarian Res. 2020;13(1):124. doi: https://doi.org/10.1186/s13048-020-00729-1
33. Massihnia D, Pizzutilo EG, Amatu A, et al. Liquid biopsy for rectal cancer: a systematic review. Cancer Treat Rev. 2019;79:101893. doi: https://doi.org/10.1016/j.ctrv.2019.101893

Recebido em 20/8/2024
Aprovado em 3/12/2024

Associate-editor: Fernando Lopes Tavares de Lima. Orcid iD: https://orcid.org/0000-0002-8618-7608
Scientific-editor: Anke Bergmann. Orcid iD: https://orcid.org/0000-0002-1972-8777