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Par

Simon MARTY

**Impact of the Sars-Cov 2 outbreak on the initial clinical presentation
of new solid cancer diagnoses: A systematic review and meta-
analysis.**

Dirigée par Mme. La Docteure Emmanuelle KEMPF

JURY

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M. le Professeur Christophe TOURNIGAND	Membre du jury
M. le Professeur Gilles CHATELLIER	Membre du jury
Mme la Docteure Ines HACINI	Membre du jury
M. le Docteur Benjamin SUBRAN	Membre du jury

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- D'une publication dans BMC Cancer : « Impact of the Sars Cov 2 outbreak on the initial clinical presentation of new solid cancer diagnoses : A systematic review and meta-analysis » par Simon Marty, Guillaume Lame, Gilles Chatelier, Etienne Guevel, Sonia Priou, Christophe Tournigand et Emmanuelle Kempf.



I. Introduction générale

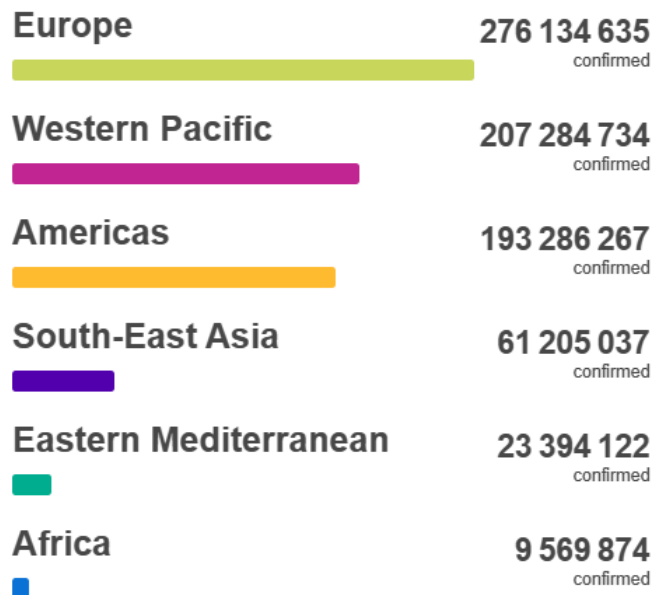
En décembre 2019, dans la région de Wuhan en Chine, apparaissent des cas de pneumopathies sévères dont l'agent infectieux semble inconnu. Rapidement identifié comme un coronavirus appelé Severe Acute Respiratory Syndrome Coronavirus 2 (Sars Cov 2), l'infection médiée par ce pathogène est nommée COVID 19 (Coronavirus Disease 2019). Se propageant tout d'abord en Chine et dans les pays frontaliers, l'OMS (Organisation Mondiale de la Santé) déclare l'état de pandémie le 11 mars 2020 (1). Par sa rapidité d'expansion à l'échelle mondiale, sa gravité clinique potentielle, et l'absence d'arsenal thérapeutique d'efficacité prouvée entraînant de nombreuses controverses dans le monde scientifique dans les premiers mois, la COVID 19 représente la plus importante crise sanitaire que le monde ait connu depuis la grippe espagnole au début du XX^{ème} siècle (2). Sur le plan clinique, cette infection se caractérise par une transmission par aérosolisation et une diversité importante de symptômes, dont la gravité dépend grandement du terrain sur lequel elle survient. Ainsi, si un tiers des patients atteints présentent des formes asymptomatiques, l'infection à Sars Cov 2 peut également se manifester dans la majorité des cas (environ 50%) par une symptomatologie dite « modérée » caractérisée par de la fièvre (45 à 80% des patients), de la toux (49 à 65% des cas), une anosmie (59% des cas), une symptomatologie intestinale avec diarrhée, douleurs

abdominales (12% des cas), une altération de l'état général, des céphalées, une angine... (3),(4). Enfin, au cours des premières vagues, environ 15% des patients développent des formes dites « sévères », et 5% de formes « critiques », conséquences de la réponse inflammatoire explosive consécutive à l'infection, caractérisées par un syndrome de détresse respiratoire aiguë et/ou des défaillances multiviscérales (encéphalite, myocardite, insuffisance rénale aiguë, insuffisance surrénalienne aiguë, insuffisance hépatique, pancréatique...) nécessitant des transferts en réanimation (5).

Devant cette situation sanitaire sans précédent, les gouvernements de plus de 90 pays mettent en place des stratégies de prévention non médicamenteuses avec plus ou moins de réactivité, dès début 2020 (6). Ces stratégies comprenaient des mesures de distanciation sociale plus ou moins strictes, allant de l'interdiction de rassemblement au confinement national, la fermeture des frontières à certains ressortissants provenant de pays particulièrement affectés, l'aération des espaces confinés, le port du masque en réunion, le lavage des mains à la solution hydro alcoolique, le dépistage obligatoire au moindre symptôme ou contact prolongé avec un cas suspect ou déclaré (7). Malgré ces mesures et l'arrivée sur le marché de vaccins ainsi que de recommandations de traitement médicamenteux, la COVID 19 reste malgré tout une infection virulente et potentiellement mortelle. En effet, l'OMS fait état, au 1^{er} octobre

2023, de 770 874 669 cas déclarés pour 6 959 303 décès, inégalement répartis à la surface du globe (Figure A) (8).

Situation by WHO Region



Source: World Health Organization

Figure A : Situation épidémique des cas déclarés de COVID 19 au 1er octobre 2023 à l'échelle mondiale

(source : Organisation Mondiale de la Santé)

Au-delà de ses conséquences propres en tant que maladie infectieuse, la prise en charge de toutes les pathologies chroniques fut impactée par les décisions politiques relatives à la prévention de la COVID 19, et la peur causée par la virulence du virus. En effet, dès les premiers mois de l'état de pandémie, par mesure de protection des populations les plus fragiles et comorbides, l'accès aux soins fut restreint aux soins les plus urgents, entraînant une déprogrammation massive des soins chirurgicaux, des consultations de suivis, des programmes de dépistage (9). Cet impact n'a pas épargné la discipline de l'oncologie.

Or, les cancers constituent l'une des premières causes de mortalité dans le monde au premier rang desquels le cancer du poumon (1,80 millions de décès par an), le cancer colorectal (916 000 décès par an), le cancer du foie (830 000 décès par an), le cancer de l'estomac (769 000 décès par an), le cancer du sein (685 000 décès par an) (10). Ils constituent des pathologies chroniques dont la prise en charge pluridisciplinaire implique des équipes chirurgicales, médicales, pharmaceutiques et d'imagerie ainsi qu'un suivi rigoureux et régulier sur le plan clinique, radiologique, et biologique. Devant la gravité de ces pathologies une fois diagnostiquées, une histoire naturelle assez bien connue, une fréquence et une mortalité importantes, de nombreux pays ont mis en place, au fil des années, des programmes nationaux de dépistages standardisés en vue de diminuer la mortalité spécifique des cancers concernés (Table A).

Table A. Liste des programmes nationaux de dépistages de cancers organisés, par pays⁽¹¹⁾.

Country	Organization (Type)	Year	Test	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
United States ¹	US Preventive Services Task Force (A)	2016	Colo or FS+FIT								
United States ¹	US Preventive Services Task Force (A)	2016	FIT, gFOBT, or FIT-DNA ¹								
United States ¹	US Preventive Services Task Force (A)	2016	CT colo or FS								
United States ¹	American Cancer Society (B)	2017	Colo								
United States ¹	American Cancer Society (B)	2017	FIT, gFOBT, or FIT-DNA								
United States ¹	Multi-Society Specialty Group (C)	2017	FIT								
United States ²	Multi-Society Specialty Group (C)	2017	Colo								
Luxembourg	Ministry of Health (A)	2016	FIT								
Switzerland ²	League Against Cancer (B)	2013	FIT/gFOBT								
Norway ¹	Cancer Registry of Norway (B)	2012	FIT								
Netherlands	NIPHE (A)	2014	FIT								
Germany ²	Federal Joint Committee (A)	2017	FIT + Colo								
Sweden	National Board of Health and Welfare (A)	2014	gFOBT								
Ireland ²	National Screening Service (A)	2012	FIT								
Austria ⁴	Austrian Cancer Care (B)	2003	FIT + Colo								
Denmark	National Board of Health (A)	2014	FIT								
Belgium	Foundation Against Cancer (B)	2016	FIT								
Canada ⁷	CTFPHC (A)	2016	FIT/gFOBT								
Australia	AGDH (A)	2016	FIT/gFOBT								
France	Institut National Du Cancer (A)	2015	FIT								
Japan	National Cancer Center (A)	2016	FIT								
Iceland ²	Icelandic Cancer Society (B)	2015	FIT								
UK	UK National Screening Committee (A)	2016	FIT								
Finland	Cancer Society of Finland (B)	2010	gFOBT								
New Zealand	Ministry of Health (A)	2017	FIT								
Italy ²	National Screening Observatory (A)	2015	FIT								
Spain	CSNHS (A)	2009	FIT								

Recommend: ■ Every year; ■ Recommend selectively: Every 2 years; ■ Do not recommend: Every 5 years; ■ Insufficient evidence: Every 10 years; ■ No interval specified.

a) Organisation des dépistages nationaux des cancers colorectaux par pays

Country	Organization (Type)	Year	Test	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
United States	US Preventive Services Task Force (A)	2016	Cyt								
United States	American Cancer Society (B)	2015	Cyt								
United States ²	American College of Obstetrics & Gynecology (C)	2017	Cyt								
United States	American College of Radiology (C)	2016	Cyt								
Luxembourg	Ministry of Health (A)	NA	Cyt								
Switzerland ²	League Against Cancer (B)	2016	Cyt								
Norway	Cancer Registry of Norway (B)	2010	Cyt								
Netherlands ³	NIPHE (A)	2017	Cyt								
Germany	Federal Joint Committee (A)	2015	Cyt								
Sweden ⁴	National Board of Health and Welfare (A)	2013	Cyt								
Ireland	National Screening Service (A)	NA	Cyt								
Austria	Austrian Cancer Aid Society (B)	2014	Cyt								
Denmark	National Board of Health (A)	2014	Cyt								
Belgium	Foundation Against Cancer (B)	2017	Cyt								
Canada ⁵	CTFPHC (A)	2011	Cyt								
Australia	Australian Government Department of Health (A)	2015	Cyt								
France ⁶	National Cancer Institute (A)	2015	Cyt								
Japan ⁸	National Cancer Center (A)	2016	Cyt								
Iceland	Icelandic Cancer Society (B)	NA	Cyt								
UK	UK National Screening Committee (A)	2012	Cyt								
Finland	Cancer Society of Finland (B)	2010	Cyt								
New Zealand	Ministry of Health (B)	2014	Cyt								
Italy	National Screening Observatory (A)	2015	Cyt								
Spain	Cancer Strategy of National Health System (A)	2009	Cyt								

Recommend: ■ Every 3 years; ■ Recommend selectively: Every 2 years; ■ Do not recommend: Every 1 year; ■ Insufficient evidence; ■ No interval specified.

b) Organisation des dépistages nationaux de cancers du sein par pays

Country	Organization (Type)	Year	Test	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+
United States	USPST final recommendation (A)	2012	PSA								
United States	USPST draft recommendation (A)	2017	PSA								
United States ¹	American Cancer Society (B)	2016	PSA								
United States ²	American Urological Association (C)	2015	PSA								
Luxembourg ³	Ministry of Health (A)	2014	PSA								
Switzerland ⁴	League Against Cancer (B)	2015	DRE, PSA								
Norway	Cancer Registry of Norway (B)										
Netherlands	NIPHE (A)										
Germany	Federal Joint Committee (A)	2017	DRE								
Sweden	NBHW (A)	2016	PSA								
Ireland	National Screening Service (A)										
Austria ⁵	Austrian Cancer Care (B)	2015	DRE, PSA								
Denmark	National Board of Health (A)										
Belgium ⁶	Foundation Against Cancer (B)	2017	PSA								
Canada	CTFPHC (A)	2014	PSA								
Australia	AGDH (A)	2017	PSA								
France	Institut National Du Cancer (A)	2016	PSA								
Japan	National Cancer Center (A)	2009	DRE, PSA								
Iceland ⁷	Icelandic Cancer Society (B)	2016	PSA								
United Kingdom	UK National Screening Committee (A)	2016	PSA								
Finland	Cancer Society of Finland (B)										
New Zealand	Ministry of Health (A)	2016	PSA								
Italy	National Screening Observatory (A)										
Spain	CSNHS (A)	2009	PSA								

Recommend: ■ Every year; ■ Recommend selectively: Every 2 years; ■ Do not recommend: No interval provided; ■ Insufficient evidence; ■ No recommendations available.

c) Organisation des dépistages nationaux des cancers de la prostate par pays

Country	Organization (Type)	Year	Test	10-19	20-29	30-39	40-49	50-59	60-69	70-79
United States ¹	US Preventive Services Task Force (A)	2012	Cyt							
United States ¹	US Preventive Services Task Force (A)	2012	Cyt+HPV							
United States ¹	US Preventive Services Task Force draft (A)	2017	Cyt							
United States ¹	US Preventive Services Task Force draft (A)	2017	HPV							
United States ²	American Cancer Society (B)	2016	Cyt							
United States ²	American Cancer Society (B)	2016	Cyt+HPV							
United States ³	American College of Obstetrics & Gynecology	2016	Cyt							
United States ³	American College of Obstetrics & Gynecology	2016	Cyt+HPV							
Luxembourg	Ministry of Health (A)	2010	Cyt							
Switzerland ²	League Against Cancer (B)	2010	Cyt							
Norway ³	Cancer Registry of Norway (B)	2010	Cyt							
Norway ³	Cancer Registry of Norway (B)	2010	HPV							
Netherlands ⁴	NIPHE (A)	2015	Cyt							
Germany ⁵	Federal Joint Committee (A)	2015	Cyt							
Sweden ⁶	National Board of Health and Welfare (A)	2014	Cyt							
Sweden ⁶	National Board of Health and Welfare (A)	2014	HPV							
Ireland ²	National Screening Service (A)	2008	Cyt							
Austria ⁷	Austrian Cancer Aid Society (B)	NR	Cyt							
Denmark ⁸	National Board of Health (A)	2014	Cyt							
Denmark ⁸	National Board of Health (A)	2014	HPV							
Belgium ⁹	Foundation Against Cancer (B)	2017	Cyt							
Canada	CTFPHC (A)	2013	Cyt							
Australia ¹⁰	Australian Government Department of Health (A)	2017	Cyt							
Australia ¹⁰	Australian Government Department of Health (A)	2017	HPV							
France ¹¹	National Cancer Institute (B)	2017	Cyt							
Japan ¹²	National Cancer Center (A)	2010	Cyt							
Japan ¹²	National Cancer Center (A)	2010	HPV							
Japan ¹²	National Cancer Center (A)	2010	Cyt+HPV							
Japan ¹²	National Cancer Center (A)	2010	HPV with cyt triage							
Iceland ¹³	Icelandic Cancer Society (B)	NR	Cyt							
UK ¹⁴	UK National Screening Committee (A)	2016	HPV							
Finland ¹⁵	Cancer Society of Finland (B)	2010	Cyt or HPV							
New Zealand ¹⁶	Ministry of Health (B)	2014	Cyt							
Italy ¹⁷	National Screening Observatory (A)	2015	Cyt							
Spain ¹⁸	Cancer Strategy of National Health System (A)	2009	Cyt							

Recommend: ■ Every 2 years; ■ Recommend selectively: Every 5 years; ■ Do not recommend: Every 3 years; ■ Insufficient evidence; ■ No interval specified.

d) Organisation des dépistages nationaux des cancers de la prostate par pays

Ces dépistages, en permettant une détection précoce des tumeurs, à des stades localisés, ont pour conséquence d'augmenter la capacité de traitement des patients entraînant une amélioration de leur pronostic en réduisant le risque de mortalité (12).

Cette organisation de prévention secondaire oncologique à l'échelle nationale fut par conséquent perturbée de manière très importante lors des premiers mois de pandémie du fait de la mise en place de mesures de confinements nationaux adjointes à la suspension des programmes de dépistage demandée par les tutelles (Table B (9)).

Table B. Liste des éventuelles mesures de distanciation sociale nationale et impact sur les programmes nationaux de dépistage de cancers dans les pays à l'étude dans notre travail

Country	Date of First National Lockdown	Cancer Screening Disruptions
Italy	09/03/2020 – 03/05/2020(13)	From March to May 2020(13)
Netherlands	from 15 March until early June 2020(14)	From March, 12, 2020 to mid May 2020(15)
Spain	14/03/2020 - 09/05/2020(16,17)	From 12/03/2020 to mid May 2020(18,19)
Turkey	29/04/2021 – 14/05/2021(20). No national lockdown in 2020.	From March 2020 to June, 1st 2020 (21)
USA	<ul style="list-style-type: none"> • California: 19/03/2020 – 15/06/2021(22) • Connecticut: 23/03/2020 – 22/04/2020(23,24) • Illinois: 21/03/2020 – 30/05/2020(25) • Kansas: 24/03/2020 – 19/04/2020(26) • Massachusetts: 24/03/2020 – 04/05/2020(27) • Michigan: 24/03/2020 – 13/04/2020(28) • New York: 22/03/2020 – 13/06/2020(29) • Oregon: 24/03/2020 – 15/05/2020(30) • Wisconsin: 24/03/2020 – 13/05/2020(31) 	Mid March to Mid July 2020(32)
Taiwan	No national lockdown(33)	No cancer screenings suspension(34)
Switzerland	17/03/2020 – 27/04/2020(35)	From mid March 2020 to 6 weeks later(36)
Germany	22/03/2020 – 20/04/2020(37)	From late March to late April 2020(38)
Portugal	18/03/2020 – 02/05/2020(39)	From mid March to May 2020(39)
China	<p>Main provinces(40):</p> <ul style="list-style-type: none"> • Hubei: 23/01/2020 - 25/03/2020 • Zhejiang: 02/02/2020 – 20/02/2020 • Xinjiang: 18/07/2020 – 26/08/2020 • Hebei: 07/01/2021 – 31/01/2021 • Shaanxi: 22/12/2021 – 16/01/2022 • Henan: 10/01/2022 – 03/02/2022 • Guangdong: 14/03/2022 – 21/03/2022 • Shanghai: 01/04/2022 – 01/06/2022 	No screening interruption
France	17/03/2020 – 11/05/2020 (41)	From mid March to 15/06/2020 (42)
Canada	<p>Main provinces:</p> <ul style="list-style-type: none"> • Ontario: 17/03/2020 – 14/05/2020 (43) • British Columbia: 18/03/2020 – 18/05/2020 (44) • Quebec: 18/03/2020 – 05/04/2020 (45) 	23/03/2020 – 26/05/2020 (24)
United Kingdom	23/03/2020 – 10/05/2020 (46)	Between March and April 2020 (47)
South Korea	No national lockdown (48)	No cancer screening suspension (49)
Japan	No national lockdown (50)	From April 7 to May 25 2020 (51)
Brazil	No national lockdown (52,53)	No population-based cancer screening programs in Brazil (53)
Singapore	07/04/2020 – 01/06/2020 (54,55)	07/04/2020 – 01/06/2020 (56)
Poland	13/03/2020-19/04/2020 (57,58)	April-May 2020 (59)
India	25/03/2020-08/06/2020 (60,61)	During 2020 Lockdown (62)

Suite aux deux premières vagues de la pandémie et aux interruptions de soins liées, l'OMS enregistrerait déjà une baisse inquiétante du

nombre de cancers diagnostiqués en Europe. En effet, à la fin de l'année 2020, la Belgique enregistrait une baisse de 44% des nouveaux diagnostics de tumeurs invasives, tandis que l'Espagne voyait une décroissance de 34% du nombre total de cancers diagnostiqués en 2020, par rapport à 2019. Sur la même période, l'Italie décrivait quant à elle une chute de 46% dans le diagnostic des seuls cancers colorectaux (63). Plus largement, à l'échelle mondiale, un travail de méta-analyse montrait qu'à l'issue des deux premières années de pandémie (2020-2021), la réalisation de dépistages systématiques avait diminué de 37% par rapport à 2019, tandis que le nombre total de cancer diagnostiqué avait, lui, diminué de 27% (64).

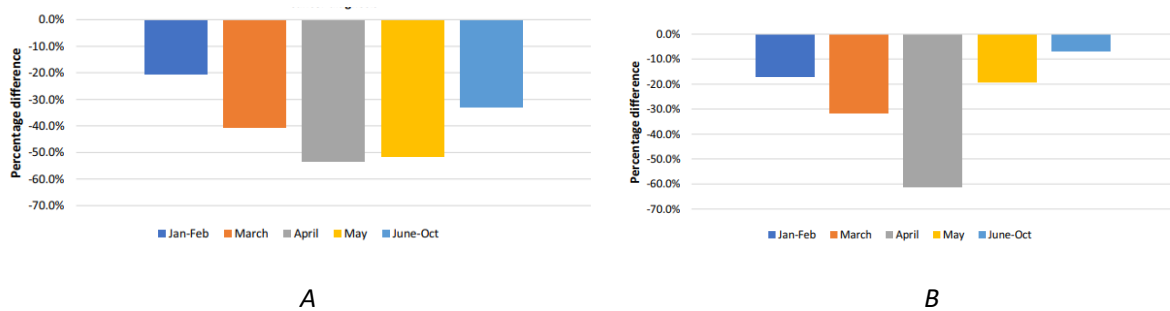


Figure B: Décroissance des tests de dépistages (A) et des diagnostics de cancer solides (B), à l'échelle mondiale, entre 2019 et 2021⁽⁶⁴⁾

Cette diminution du nombre de nouveaux cas de cancer lors du début de la pandémie a fait craindre un retard accru de diagnostic des cancers, et donc, un diagnostic réalisé à un stade de dissémination

tumorale plus avancée ainsi qu'une mortalité plus élevée en lien avec ces diagnostics tardifs comme le montrent de nombreuses études de modélisation (65–67). Notre travail avait pour objectif, via la conduite d'une revue systématique de la littérature et d'une méta-analyse, d'évaluer l'impact de la crise COVID 19 sur le stade de dissémination tumorale des cancers solides nouvellement diagnostiqués dans les populations adultes à l'échelle mondiale, par rapport à la situation pré-pandémique.

II. Résumé et indexation en français

Impact de la crise COVID 19 sur la présentation clinique initiale des cancers solides nouvellement diagnostiqués : Une revue systématique de la littérature et une méta-analyse.

Résumé :

Contexte : Les perturbations de soins causées par la crise COVID 19 ont pu impacter la présentation initiale des cancers solides nouvellement diagnostiqués sur cette période ainsi que leur pronostic. Le but de cette revue systématique de la littérature était de comparer la distribution globale des stades des cancers solides avant et après les premières vagues de la pandémie.

Méthode : Une revue systématique de la littérature a été réalisée en suivant les recommandations PRISMA et MOOSE, par deux investigateurs indépendants au travers des publications disponibles sur MEDLINE et EMBASE. Une méta-analyse a été conduite afin de comparer le taux de métastases au diagnostic de cancers solides avant et après les premières vagues de la pandémie. Des analyses en sous-groupes ont été menées par type de cancer, et par localisation géographique de l'étude. L'hétérogénéité entre les études et les différences entre sous-groupes ont été vérifiées par des tests I^2 et X^2 .

Résultats : Des 2013 articles extraits par l'équation de recherche, 58 ont été inclus dans l'analyse finale, représentant 109 996 patients. Le taux de présentation métastatique au diagnostic était significativement plus important après les premières vagues de la pandémie (pooled OR: 1.29 (95% CI, 1.06-1.57), I^2 : 89% (95% CI, 86-91)). Les analyses en sous groupes par type de cancer ont révélé significativement plus de métastases au diagnostic pour les cancers du sein et les cancers gynécologiques (OR: 1.51 (95% CI 1.07-2.12) et OR: 1.51 (95% CI 1.04-2.18) respectivement). Les autres types de cancers

ne révélaiet pas de modifications significatives. Les analyses en sous groupes par localisation géographique des études montraient significativement plus de métastases au diagnostic en Italie (OR (95% CI) : 1.55 (1.01-2.39)) et en Espagne (OR (95% CI) : 1.14 (1.02-1.29)). Au contraire, moins de métastases au diagnostic ont été notifiées à Taiwan (OR (95% CI) : 0.51 (0.28-0.93)) et au Canada (OR (95%CI) : 0.14 (0 .07-0.29)). La répartition des stades I-II VS III-IV et I-II VS III ne montrait quand à elle pas de différence notable par pays ou par type de cancer.

Conclusion : Malgré une hétérogénéité importante entre les études, notre méta-analyse a démontré un taux plus important de métastases au diagnostic après la pandémie COVID 19. La mise en place de mesures préventives de distanciation et le report des soins peuvent contribuer à expliquer ce résultats.

Spécialité :

[Médecine Interne](#)

Mots clés français :

[COVID 19](#), [Système de santé](#), [Détection précoce des cancers](#), [Recherche sur les système de soins](#), [Métastases](#), [Stadification des cancers](#).

Forme ou Genre :

fMeSH : Dissertation universitaire

Rameau : Thèses et écrits académiques

III. Résumé et indexation en anglais

**Impact of the Sars-Cov-2 outbreak on the initial clinical presentation of new solid cancer diagnoses:
a systematic review and meta-analysis**

Abstract:

Background: The COVID-19 pandemic disrupted healthcare systems which might have impaired the initial clinical presentation and the related prognosis of new solid tumor patients. The aim of this systematic review was to determine and compare the initial tumor stage of solid cancer diagnoses before and after the first waves of the Sars Cov-2 outbreak.

Methods: Following the PRISMA and MOOSE guidelines, a systematic review on the tumor stage of new solid cancer diagnoses before and after the COVID-19 pandemic was performed by independent reviewers from the published literature in MEDLINE and EMBASE. A random-effects meta-analysis on the rate of metastatic tumors was conducted to compare the rate of metastatic tumors at initial presentation before and after the initial pandemic waves. Subgroup analyses were performed according to the primary tumor site, and to the study country. Interstudy heterogeneity and subgroup differences were assessed with I^2 and X^2 tests, respectively.

Results: From 2,013 studies published between January 2020 and April 2022, we included 58 studies with 109,996 patients. The rate of metastatic tumors was higher after the COVID-19 outbreak than before (pooled OR: 1.29 (95% CI, 1.06-1.57), I^2 : 89% (95% CI, 86-91)). For specific cancers, common ORs reached statistical significance for breast (OR: 1.51 (95% CI 1.07-2.12)) and gynecologic (OR: 1.51 (95% CI 1.04-2.18)) cancers, but not for other cancer types. According to countries, common OR (95% CI) reached statistical significance only for Italy: 1.55 (1.01-2.39) and Spain:1.14 (1.02-1.29). Conversely, lower metastatic rates were found in Taiwan (OR (95% CI) : 0.51 (0.28-0.93)) and in Canada (OR (95%CI) : 0.14 (0 .07-0.29)).

Rates were comparable for stage I-II versus III-IV in studies for which that information was available, and for stages I-II versus stage III in studies that did not include metastatic patients.

Conclusions: Despite inter-study heterogeneity, our meta-analysis showed a higher rate of metastatic tumors at diagnosis after the pandemic. The burden of social distancing policies might explain those results, as patients may have delayed seeking care.

English keywords:

COVID-19, Delivery of Health Care, Early detection of cancer, Health Services Research, Neoplasm Staging, Neoplasm Metastasis.

Publication type:

MeSH : Academic Dissertation

IV. Liste des abréviations

- Sars-Cov 2: Severe Acute Respiratory Syndrome Corona Virus 2
- COVID 19: Coronavirus Disease 2019
- WHO: World Health Organisation
- OMS: Organisation Mondiale de la Santé
- OR : Odd Ratio
- CI : Confidence Interval
- IC : Intervalle de confiance
- VS : Versus
- PRISMA : Preferred Reporting Items for Systematic Review and Meta-Analyses
- MOOSE: Meta-Analysis of Observational Studies in Epidemiology
- MeSH: Medical Subject Headings
- NIH: National Institute of Health
- E.G.: Exempli gratia
- M+: Metastatic
- M-: Non metastatic
- N+: Node invasion
- N0: No node invasion
- B: Breast cancer
- C: Colorectal cancer
- M: Melanoma
- G: Gynecologic cancer
- P: Prostate cancer
- L: Lungs cancer
- Ga: Other gastrointestinal cancers
- G-U: Genito-Urinary cancers
- O: Other types of cancers
- NA: Not Applicable
- UK: United Kingdom

- USA: United States of America
- PMID: PubMed Identifier.
- SRAS Cov: Syndrome respiratoire Aigu Sévère lié au Coronavirus

Background

In 2020, the COVID-19 pandemic disrupted healthcare systems worldwide, as a result both of the pandemic itself and the strain it imposed on services, and of the range of social distancing policies that were implemented and may have affected care-seeking behaviors. In cancer care, screening programs were suspended in many countries, and care strategies were sometimes adapted to avoid exposing patients to COVID-19 infection, and to reduce the burden on intensive care units. Patients may also have avoided consulting for fear of being contaminated. As a result, meta-analyses suggest that screening decreased by 40 to 50% , and that overall, cancer diagnoses fell by 27% in January-October 2020 compared to the pre-COVID-19 period(68,69).

Although recovery plans have been implemented in many countries, it is possible that patients with new cancers whose initial care was delayed could present more advanced tumors, with poorer prognosis. Indeed, modeling studies have anticipated thousands of additional cancer-related deaths in the coming years due to delays in diagnosis and treatment, resulting in tens of thousands of total years of life lost compared with pre-pandemic setting(70).

The aim of this systematic review of the literature with meta-analysis was to compare the proportion of metastatic presentations, and the distribution of initial tumor stage at diagnosis, before and after the COVID-19 outbreak, for patients with solid cancers

1 : Material and method

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA 2020) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.(71),(72)

1.1 *Data sources, literature searches and eligibility criteria*

We searched PubMed and Embase databases for English-language original articles published between January 2020 and April 2022 that included information on the impact of the COVID-19 pandemic on solid malignant tumor stage, using Medical Subject Headings (MeSH) terms and free words. The complete search equation is available in Supplementary materials, Appendix S1. We screened the list of retrieved articles by evaluating titles first, then abstracts, and finally full texts. At each step, two independent investigators evaluated each article. A third independent investigator settled disagreements. We included articles in English that compared cancer stages at diagnosis before versus after the Covid-19 outbreak, using any relevant cancer staging guideline. We excluded reviews, editorials, posters, letters, and guidelines. Full inclusion and exclusion criteria are available in Appendix S2.

1.2 *Data collection and risk of bias assessment*

For each article, two independent investigators collected items of interest which are summarized in Appendix S3. In the event of a discrepancy, a third independent investigator

settled the issue. We did not contact any study author. We classified primary tumor types as displayed in Appendix S4. We assessed the risk of bias of the included studies with the NIH Quality Assessment Tool for Observational Cohort and Cross-sectional Studies.(73)

1.3 *Data analysis*

We used the rate of metastatic tumors for comparing cancer presentation before and after the initial COVID-19 pandemic waves. We calculated odds ratio (OR) and 95% confidence intervals (CI) for each study, and we then pooled these individual ORs using a random-effects meta-analysis. Subgroup analyses were performed according to the primary tumor site (when this information was available), and to the study country.

We conducted meta-analysis across all studies and at the subgroup level using the Mantel-Haenszel method. Because we expected heterogeneity between studies, we used the Hartung-Knapp method to calculate CIs on the main effect estimate, with a variance correction.(74,75) We computed prediction intervals for exposure effect based on Hartung and Knapp's method.(76) Results were graphically represented in forest plots. The extent of interstudy heterogeneity and subgroup differences were assessed with the Cochran I^2 statistics and X^2 tests, respectively. Between-study variance τ^2 was assessed using the Sidik and Jonkman's approach and the Q-Profile method for τ^2 's CI.(77,78) We applied a continuity correction of 0.5 in studies with zero events in one arm.

When articles mentioned missing data or unknown status for some patients, we ignored those patients. When studies overlapped, we only included the study with the broadest inclusion criteria.(79) In situ tumors were excluded from the analysis.

For analyses where more than ten studies could be included, we plotted funnel plots and conducted Thompson and Sharp's arcsine test to assess the presence of small study effects.(80,81)

Using the same methods, we performed meta-analysis on the rate of stage I-II versus III-IV for the studies where this information was available. When studies mentioned 'advanced stages' with no more detailed information, we counted the 'advanced' patients as stage IV when a separate 'locally advanced' category was also available. These data were then included in the first analysis of metastatic vs non-metastatic status. If no separate 'locally advanced' category was available alongside 'advanced', we could not know if these 'advanced' patients were stage III or IV, and these data were included in the 'stage I-II vs III-IV' analysis.

Finally, for studies that did not include metastatic patients (e.g., studies that focused on patients undergoing surgery), we performed a separate meta-analysis comparing stage I-II versus stage III.

All analyses were conducted using R v.2.2.2 (The R project for statistical computing, www.r-project.org) and the *meta* package (v6.2.1.).(82) No ethics committee approval and no patient consent were necessary because the study was restricted to publicly available data.

2 : Results

2.1 *Study characteristics*

We identified 2,013 studies published between January 2020 and April 2022, and included 58 studies in our meta-analysis (Figure 1, Supplementary Table S1). These articles covered Europe, Asia, North and South America (Supplementary Figure S1). The quality assessment of included studies is presented in Supplementary Table S2. For each study location, lockdowns and cancer screening postponement were summarized in Supplementary Table S3. Breast cancer was the most represented cancer type.

Forty-five studies (98,307 patients) compared metastatic stages IV versus non-metastatic stages I-II-III; Nine studies (7316 patients) compared stages I-II versus III-IV (some articles contributed to both the first and the second analyses) and six (4,373 patients) compared stages I-II versus III without including metastatic patients. The number of patients included per study ranged from 44 to 54, 828 (Supplementary Table S1) .

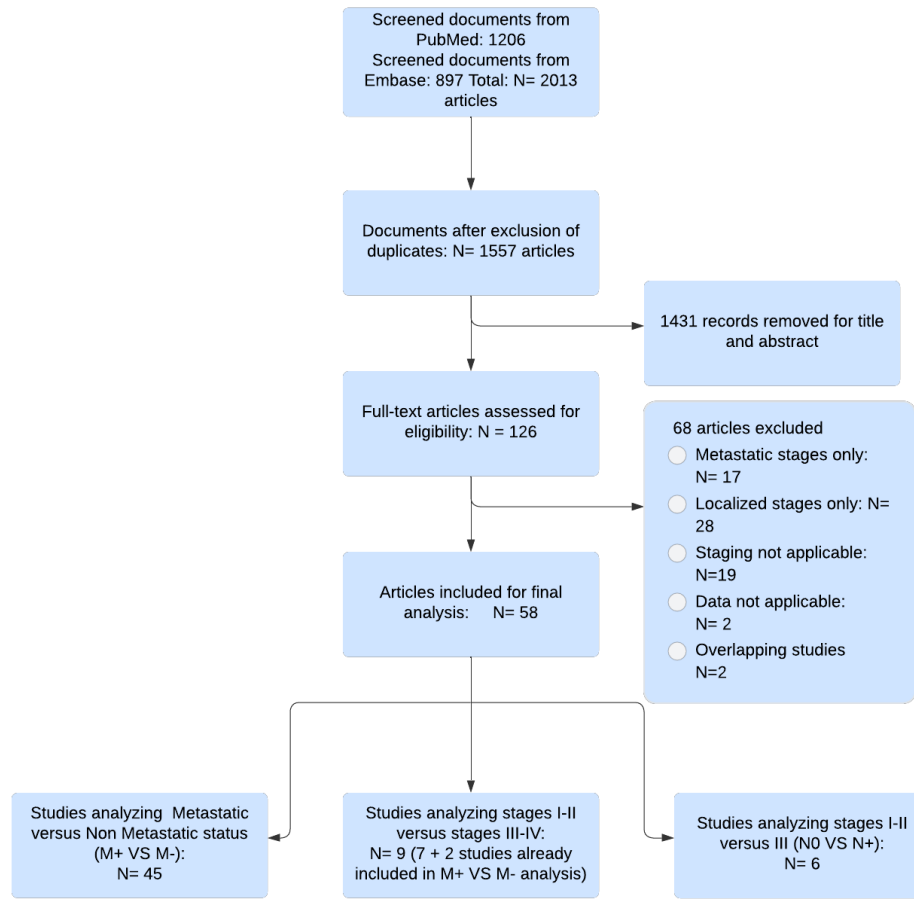


Figure 1: Study selection flowchart.

Two instances of overlapping studies were identified. In the case of two Dutch register-based studies, we kept the study that included all patients over the one that focused on screening and included only patients aged 50-74.(83,84) In the case of two Italian studies, one monocentric and one multicentric that included the previous center, we kept the multicentric study.(85,86)

2.2 *Metastatic versus non-metastatic:*

In the 45 studies that contained information on metastatic stage shift, the OR (95% CI) on metastatic stage after vs before the COVID-19 outbreak reached 1.29 (1.06-1.57), indicating a higher probability of patients being metastatic after the outbreak (Figure 2). Heterogeneity between studies was high, with a I^2 of 89% (95% CI, 86-91) and ORs varying from 0.14 to 12.07. Funnel plot showed uneven distribution of small studies (Figure 3), but the arcsine test was not significant ($p = 0.25$).

In subgroup analysis per country, results reached statistical significance for Italy (seven studies) and Spain (one study), with ORs of 1.55 (1.01-2.39) and 1.14 (1.02-1.29) respectively (Figure 3). In other countries with more than one study, ORs were 1.65 (0.37-7.32) for Turkey, 1.14 (0.46-2.84) for the Netherlands, 1.88 (0.78-4.53) for the US, 1.48 (0.00-1135,67) for France, 0.96 (0.26-3.53) for Germany, 1.36 (0.26-7.20) for Portugal, 0.91 (0.15-5.57) for China, 1.77 (0.76-4.10) for the United Kingdom, and 1.24 (0.75-2.04) for South Korea.

Conversely, lower metastatic presentations were found in Taiwan (OR (95% CI) : 0.51 (0.28-0.93)) and in Canada (OR (95%CI) : 0.14 (0.07-0.29)).

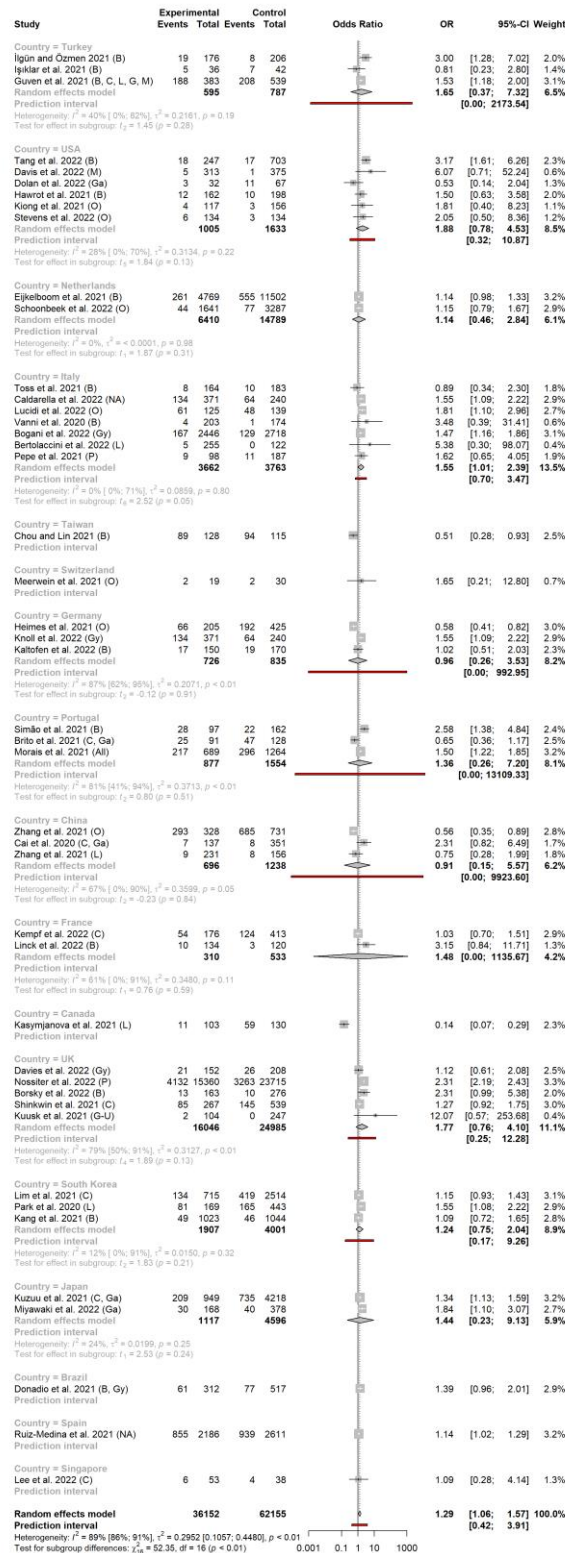


Figure 2: Metastatic tumor rates before and after the Sars Cov2 outbreak, according to study country.

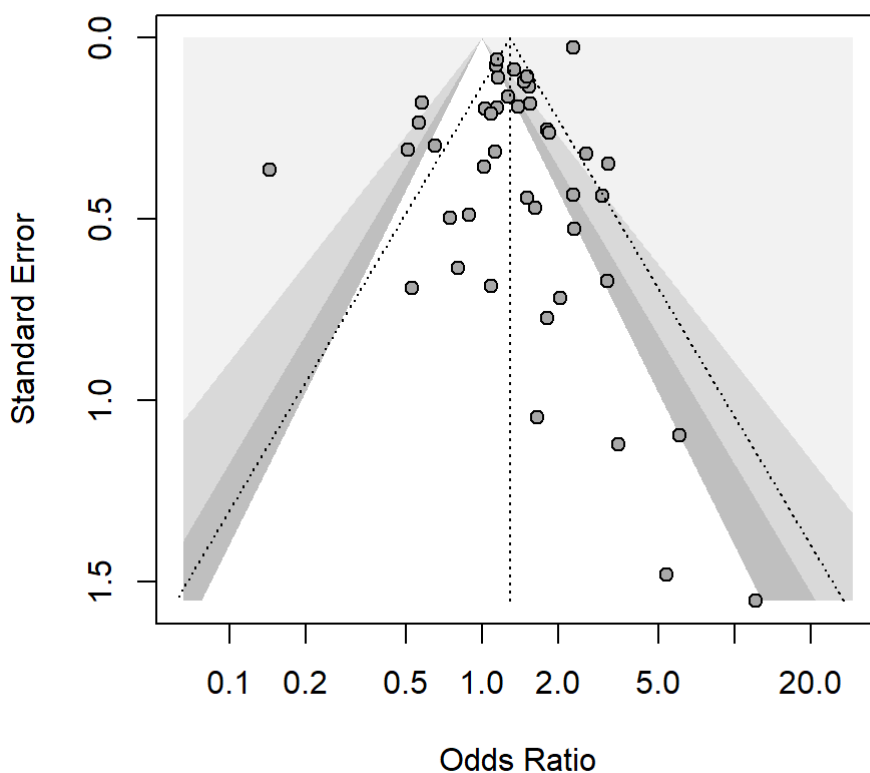


Figure 3: Funnel plot for assessment of study bias.

In subgroup analysis per location, the related OR reached statistical significance for breast and gynecologic cancers: 1.51 (1.07-2.12) and 1.51 (1.04-2.18) respectively (Figure 4). OR for other cancer types did not reach statistical significance: 0.79 (0.18-3.52) for lung cancer, 1.15 (0.89-1.49) for colorectal cancer, 1.45 (0.62-3.42) for other types of digestive cancers, 2.26 (0.51-10.05) for prostate cancer, 12.07 (0.57-253.68) for genito-urinary cancer (one study only), 2.49 (0.00-84469.69) for melanomas, and 1.01 (0.59-1.75) for other types of cancers ($X^2 = 24.60$, $p < 0.01$) (Figure 4a). The funnel plot for breast cancer (the only cancer type with more than ten studies) is available in Supplementary material (Figure S2). Arcsine test was non-significant ($p = 0.76$).

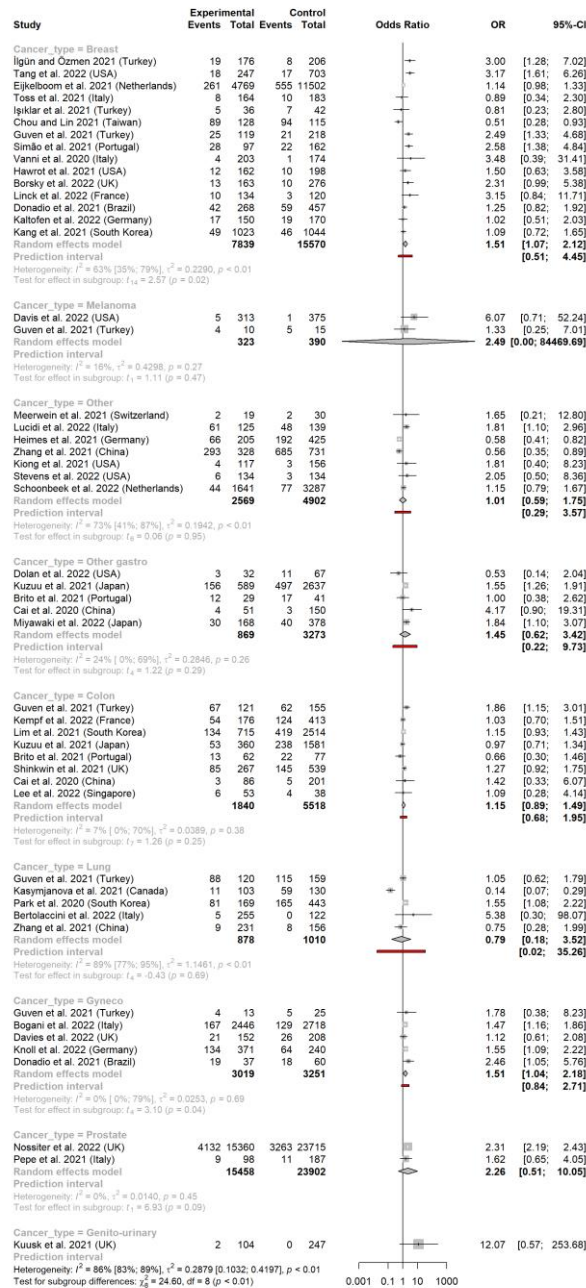


Figure 4: Metastatic tumor rates before and after the pandemic, according to cancer type.

2.3 Localized versus advanced cancer (Stages I-II vs III-IV)

In the analysis of localized versus advanced cancer stages (i.e., stages I-II vs III-IV), the pooled OR was 1.48 (0.84-2.62) (Figure 5). None of the subgroup analyses per location or per country reached statistical significance (Figures 5 and 6), except for the only Spanish study included in the stage I-II vs III-IV analysis (OR (95%): 1.17 (1.03; 1.31)). Heterogeneity was high, with I^2 51% (0-77) and ORs varying between 0.13 and 10.67

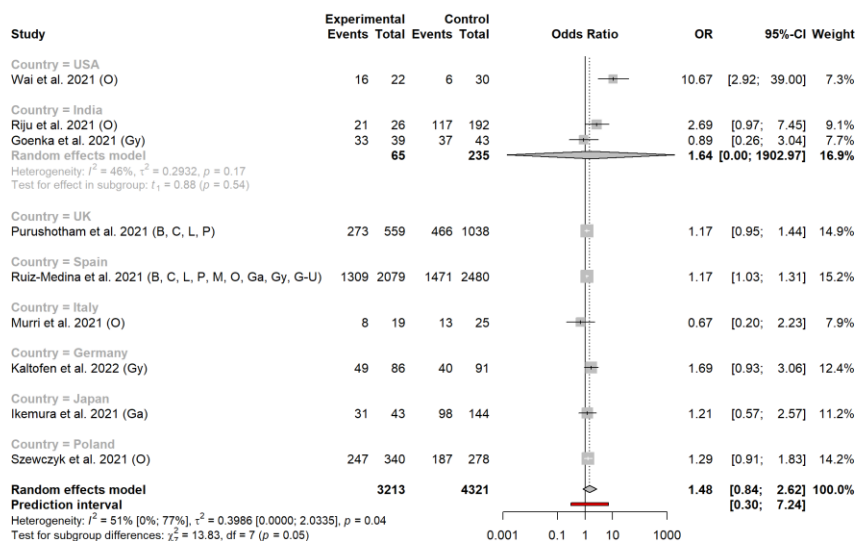


Figure 5: Rates of stage I-II versus III-IV before and after the pandemic according to study country.

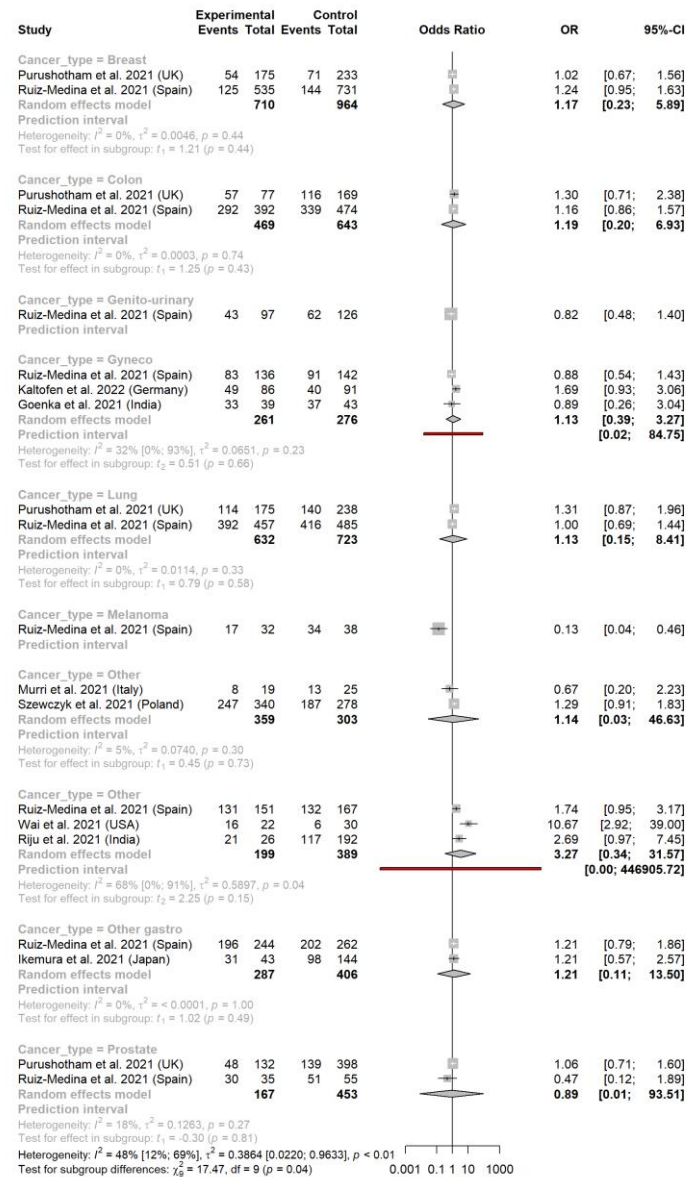


Figure 6: Rates of stage I-II versus III-IV before and after the pandemic according to cancer type.

2.4 Studies with no metastatic patients (Stages I-II vs III)

In the analysis of Stages I-II vs III, in studies that did not include metastatic patients, the pooled OR was 1.32 (0.92-1.89) (Figures 7 and 8).

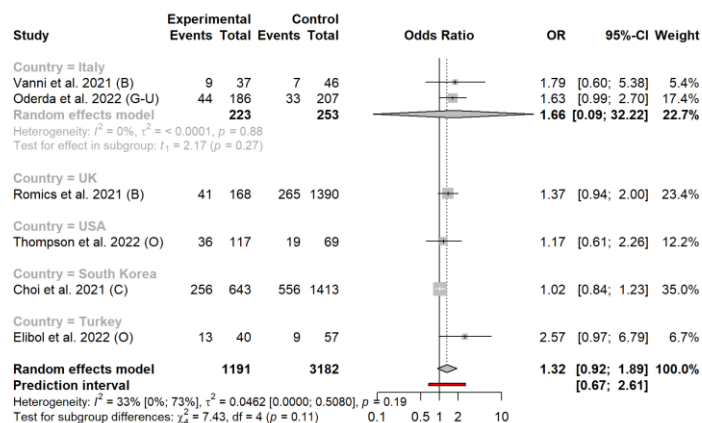


Figure 7: Rates of stage I-II versus III before and after the pandemic according to study country.

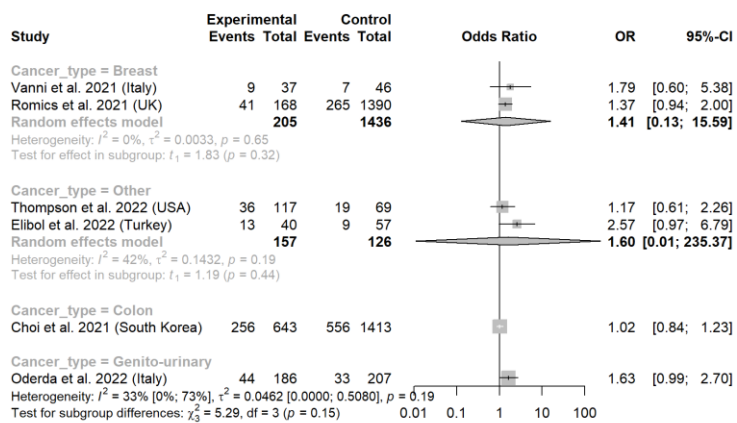


Figure 8: Rates of stage I-II versus III before and after the pandemic, according to cancer type.

3 : Discussion

We have reviewed published evidence on the impact of the Covid19 outbreak on cancer stages at diagnosis. The results of the main analysis (45 studies) showed an increased rate of metastatic stages at initial clinical presentation, for new solid cancer cases, after compared to before the COVID-19 outbreak. Subgroup analyses yielded significant results for breast and gynecologic cancers, and for Italy and Spain. Secondary analyses on Stages I-II vs III-IV (nine studies) and Stages I-II vs III (for the six studies that excluded metastatic patients) yielded non-significant results.

Based on these results, one may conclude that the pandemic has been associated with more severe forms of cancer at diagnoses. However, we noticed large variations between countries, as well as between tumor locations.

This heterogeneity is still present in more recent observational studies. In the US, Berrian *et al.* found a 21.4% increase in *de novo* metastatic disease in colorectal, lung, prostate, and breast cancers.(87) In Brazil, Resende *et al.* showed that stage IV breast cancer diagnoses were more frequent post-COVID than pre-COVID period (2018-2019). Indeed, advanced stages represented 16,9% of patients during COVID 19 pandemic versus 12,7% in the pre-pandemic period.(88)

Yet, other studies did not encounter significant differences in cancer stages. For example, studies found significant stage shifts for melanomas in the US and Greece, for lung cancer in the UK and for genito-urinary cancers in Iran.(89–93) For colorectal cancer, stage shifts were absent in Canada and the US but noticeable in Italy and South Korea.(94–97) In a systematic review, Pararas *et al.* analyzed stage shifting for colorectal cancer. They noted a significant

increase in the number of patients presenting with *de novo* metastatic neoplasms during the pandemic (OR 1.65, 95% CI 1.02–2.67).(98) We found a positive but non-significant association between the Covid19 pandemic and *de novo* metastatic colorectal cancer, but our analysis included less patients for this location, which may explain the difference in findings.

In our study, Italy and Spain were associated with significant increase of *de novo* metastatic tumor stages. In the case of Italy, such an increase might be due to the number of studies included (seven studies including 7,423 patients, versus five for the UK, six for the US and one to three for other countries). National screening programs for breast, colorectal and cervix cancers were stopped from March 2020 and resumed in May 2020, with differences between regions(99). Overall, the number of screening invitations sent was 15 to 20% smaller in 2020 than in 2019.(99) These disruptions could partly explain the excess of metastatic cases observed in Italy.(100,101) We also observed a significant increase in metastatic stages in Spain. However, we included only one Spanish study, limited to Malaga's region. Spanish national screening programs for breast and colorectal cancer were paused during the pandemic, which could have contributed to this outcome. More recent Spanish studies have obtained contrasting results.(19,102)

We found a significantly lower presence of metastatic stages at diagnosis after the COVID-19 outbreak in Taiwan and Canada. We included only one small study from each of these countries. In Taiwan, there was no national lockdown or interruption to screening programs. Indeed, Taiwan could draw on its experience of the 2003 SARS pandemic, and applied early policies of travel regulation, testing, and prevention, avoiding lockdowns and screening postponements.(103),(104) For Canada, we included a single study about lung cancer in

Quebec. In the same province, Ramanakumar *et al* did not find any significant difference in Stage IV for lung cancer before and after the pandemic.(105)

We found significantly more metastatic stages at diagnosis after the Covid-10 outbreak for breast and gynecological cancers. In both cases, we included multiple large studies (15 studies with 23,409 patients for breast cancer, 5 studies with 6,270 patients for gynecological cancers). In both cases, interruptions of screening programs may have contributed to the result.

From a general point of view, our results suggest that cancer care disruptions such as national lockdowns and national screening programs postponement led to more severe cancer cases with more metastasis at diagnosis. Unfortunately, these findings only give weight to the dark projections obtained in modelling studies, which anticipate an increase in cancer-related deaths (106–108) Lockdowns and interruptions to screening programs were probably only one factor contributing to the decrease in diagnoses. Patients feared Covid-19 infection, sometimes more than cancer (45), which can explain the prolonged impact on care seeking behaviors(109–111)

We conducted a systematic review of the academic literature, with dual, blinded study selection and data extraction. We covered all cancer types and regions. We also analyzed studies per cancer type and per country, to account for the possibility of different impacts of the pandemic. We included a large number of studies, covering 109,996 patients over 19 countries. However, some limitations must be taken into consideration when considering our findings.

Many studies in our review were small and monocenter. Researchers in areas most affected by the pandemic may have been more prone to report observational data, generating a publication bias (although this was not detected in our analyses). Monocentric studies also cannot account for potential reconfigurations in care trajectories, with some hospitals attracting more cancer patients during the pandemic while others focused on Covid-19 care. Only a minority of studies were population-based, which is the only way to mitigate these issues. When analyzing studies by country, we could not account for variations between regions, including the level of restrictions imposed (e.g., between American states).

We also noticed methodological differences. The way pre- and post-Covid time periods were defined varied between studies. Some studies focused on a short period at the apex of the pandemic, when screening programs stopped, and their area was under lockdown. It is likely that only the most serious patients presented to hospital at these times, increasing the rate of advanced tumors while the absolute number of patients decreased. Other studies defined the COVID-19 period more broadly. Data sources were also heterogeneous in our sample. A few studies were based on registries, which normally guarantee good data completeness and reliability. Other studies mixed data sources, used EHRs or claims data. This may have affected both completeness and quality of the data.

Finally, we only included English sources, and focused on full articles. Data may also have been shared in other languages, and studies presented as conference abstracts may not have been published as full articles.

Despite these limitations, our results suggest that national cancer screening programs should be maintained in high-risk populations even during infectious outbreak waves. After the disruptions, platforms of rapid cancer diagnosis might compensate the interruptions of

screening programs and clear diagnosis backlogs. The issue of how cancer care recovers from the pandemic would require population-based studies. Such studies are likely to be available only once registries have been updated, which may take some time.(112). These studies should also look at the evolution of patient survival, given the dark picture painted by modeling studies. Finally, the data we analyzed comes overwhelmingly from high-income countries. Analyzing outcomes in low- and middle-income countries is important to understand how their healthcare systems have worked to mitigate the pandemic impact.

4 : Conclusion

The COVID-19 outbreak has affected cancer management around the world. This meta-analysis of 58 articles from 19 countries showed an increased rate of metastatic stages at initial clinical presentation for new solid cancer cases diagnosed after the COVID-19 outbreak, with variations between cancer types and between countries. Future studies on the long-term consequences of the pandemic should also assess the impact on patient survival.

V. Conclusion Générale

Cette étude est, à notre connaissance, la première revue systématique de littérature et méta-analyse s'intéressant aux différences de présentation diagnostique pour les cancers solides à l'échelle mondiale, avant et après les premières vagues de cette pandémie. Les principaux résultats retrouvaient une augmentation significative de 29% (OR = 1,29 (Intervalle de Confiance (IC) 95% 1,06-1,57)) des présentations métastatiques au diagnostic pour les cancers solides dans les populations adultes après les premières vagues de COVID 19 par rapport aux périodes antérieures, et avec des disparités importantes selon les pays ou le type de cancer à l'étude. Ainsi, les résultats retrouvaient une augmentation de 51% des tumeurs solides métastatiques au diagnostic pour les cancers du sein (OR= 1,51 (IC95% 1,07-2,12)) et les cancers gynécologiques (OR=1,51 (IC95% 1,04-2,18)), par rapport aux périodes antérieure, tandis que les autres types de cancers étudiés n'étaient pas concernés de façon significative. Concernant les localisations géographiques, l'Italie et l'Espagne voyaient leur nombre de cancers métastatiques augmenter de 55% (OR = 1,55 (IC95% 1,01-2,39)) et 14% (OR = 1,14 IC95% (1,02-1,29)) respectivement, par rapport à 2019.

Ces résultats s'expriment en grande partie comme des conséquences très probables des modifications de soins et des mesures de distanciation sociale survenues pendant la COVID 19, à l'image des confinements nationaux et des arrêts des dépistages de masse. Au contraire, un nombre moins important de cas métastatique au diagnostic était notifié à Taïwan et au Canada avec une baisse de 49% (OR = 0,51 (IC95% 0,28-0,93)) et 86% (OR = 0,14 (IC95% 0,07-0,29)) en 2020 par rapport à 2019, respectivement. Une telle baisse des présentations métastatiques peut s'expliquer, dans le cas de Taïwan, par une mise en place rapide des mesures de régulation des flux de transports internationaux, de tests de masse et de prévention de la transmission du virus s'appuyant sur l'expérience de l'épidémie de Sars cov survenue en 2003 dans le pays (113). Les résultats canadiens sont, quant à eux, plus difficilement interprétables, compte tenu du peu de patients inclus (n = 233) et du caractère monocentrique de l'article étudié.

Bien que la majoration relative du nombre de présentations métastatiques semble intimement liée aux suspensions des dépistages nationaux et aux confinements survenus au pic de la pandémie, certaines études montrent que de nombreux patients ont continué à éviter les hôpitaux après la reprise normale des soins (114). La peur de l'infection était le principal facteur évoqué, intriqué de manière étroite

aux répercussions que celle-ci pourrait avoir si une pathologie chronique telle qu'un cancer solide à un stade avancé venait à être découverte : peur d'une plus faible immunité face au virus, peur d'un report de l'instauration d'un traitement du fait de l'infection ... (114,115). Ce retard au diagnostic médié par la peur du virus et la poursuite de l'isolement malgré la fin des mesures restrictives pourrait amplifier l'impact de la pandémie elle-même sur la gravité des cancers solides nouvellement découverts, et leur évolution prévisible. En effet, des études de modélisation prévoient une surmortalité significative concernant les néoplasies solides, à l'horizon 2030. En Angleterre, l'équipe de Duffy prédit une surmortalité d'environ 700 cas par an concernant le seul cancer du sein, en lien direct avec le retard diagnostic occasionné par la poursuite de l'isolement malgré la fin du confinement national survenu entre mars et mai 2020 (106). Aux Etats-Unis, l'équipe d'Alagoz prévoit, quant à elle, un excès global de mortalité de 2 487 cas pour le cancer du sein, tandis que Sharpless compte jusqu'à 10 000 morts supplémentaires pour les cancers du sein et colorectaux cumulés (65,116). Selon les études, l'excès de mortalité mesuré en 2030 au Royaume Uni et aux Etats Unis, variera entre 1 et 10%, sans différence notable selon l'ethnie du patient (65–67).

Cette surmortalité n'étant pas négligeable, il convient d'instaurer des stratégies afin de diminuer le retard diagnostique si une situation

similaire à la pandémie COVID-19 venait à se reproduire. Les résultats de notre étude plaideraient, dans la mesure du possible, pour une continuité des dépistages en temps de pandémie. Si cela s'avérait toutefois impossible, une des solutions évoquées par de nombreuses études serait une meilleure utilisation de la télémédecine à des fins de dépistage contre les cancers (117). Par exemple, aux Etats-Unis, l'équipe de Gorin suggère d'améliorer les recours aux téléconsultations incitant les patients à effectuer plus de dépistages à la maison pour les cancers colorectaux et les cancers du col de l'utérus (114). L'équipe de Parker a, quant à elle, démontré que les femmes concernées par le dépistage des cancers du col de l'utérus ont préféré, durant la pandémie COVID-19, effectuer ce dépistage à domicile du fait de la peur de contracter l'infection (41,3%), de la difficulté d'obtenir un rendez-vous en temps de crise sanitaire (21,7%), et d'avoir plus de temps pour s'occuper de leur santé en temps de confinement (12%) (115). Les populations les plus âgées pourraient, quant à elles, bénéficier d'une éducation à la télémédecine, ce recours étant essentiellement utilisé par les populations les plus jeunes (118). Enfin, une utilisation facilitée de l'intelligence artificielle médicale semble pouvoir être une solution afin de rattraper un retard diagnostic occasionné par les perturbations de soins survenues en temps de pandémie, en permettant une détection rapide des lésions

cancéreuses ainsi qu'un triage plus efficace des patients pour les suites de prises en charge (119,120).

La crise COVID 19 et les perturbations de soins qui en résultent pourraient être riches d'enseignements dans un monde où les conflits armés sont de plus en plus nombreux et globaux, entraînant bien souvent d'importantes ruptures de suivis chez les patients atteints de pathologies chroniques, et notamment de cancers (121). Par exemple, fin 2020, en pleine crise COVID 19, 82 millions de personnes se sont vues contraintes de quitter leur pays du fait de contexte de guerre (122). En Ukraine, depuis février 2022 et l'annexion par la Russie, plus de 3 millions de personnes ont fui le pays. Les patients atteints de cancer résidant toujours sur le territoire ukrainien font face à un retard de prise en charge majeur et inévitable, du fait des dommages causés aux infrastructures de soins, de la réquisition des services pour la prise en charge des blessés de guerre, de la peur de sortir des habitations en lieu découvert, du manque de moyen de transport ... Ainsi, l'équipe de Calgevic, estime qu'un retard de 4 mois dans la prise en charge des cancers en Ukraine en ce temps de guerre mènera à un surplus annuel de 676 morts pour le cancer de la vessie, 663 pour le cancer du côlon, 1 118 pour le cancer du sein, 306 pour les cancers du nasopharynx, et 848 pour le cancer du col de l'utérus dans les prochaines années (123). De même, l'émergence d'un conflit armé

entre Israël et la Palestine laisse présager de conséquences néfastes liées au retard de prise en charge des pathologies chroniques et notamment des cancers, dont le bilan des pertes viendra s'ajouter à celui des disparus civils et militaires. Limiter les décès « indirects » en temps de guerre apparait donc comme un enjeu essentiel au cours des prochains mois et années, et en ce sens, l'expérience acquise lors des crises sanitaires mondiales doit se rendre au service de la communauté internationale et des états en détresse.

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Figure S1: Location of included studies

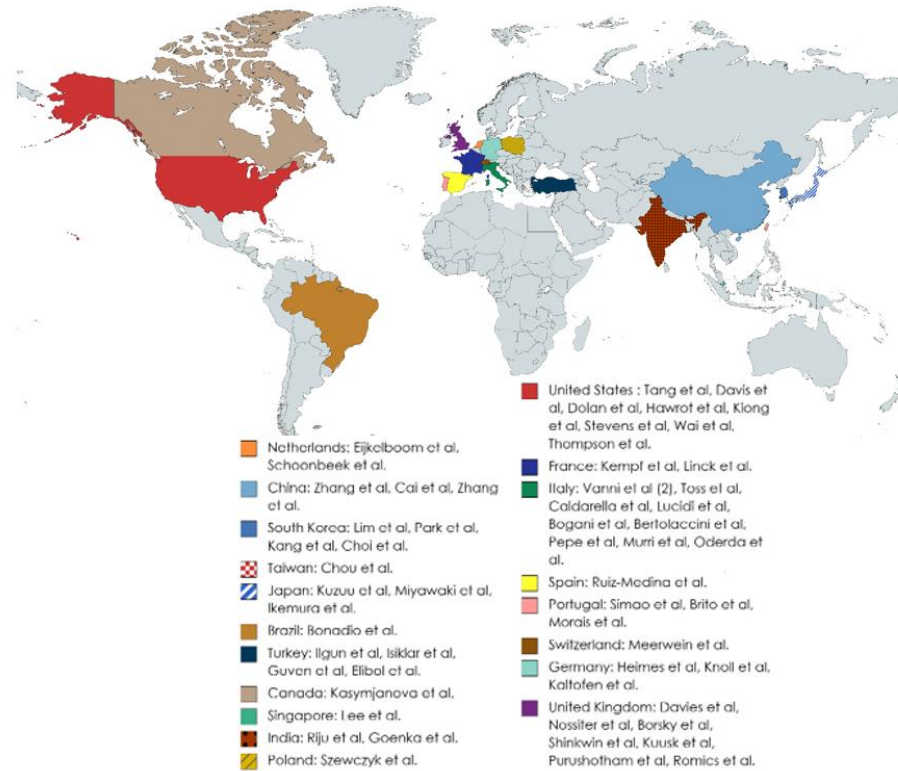


Figure S2. Funnel plot for subgroup metastatic vs non-metastatic analysis on breast cancer

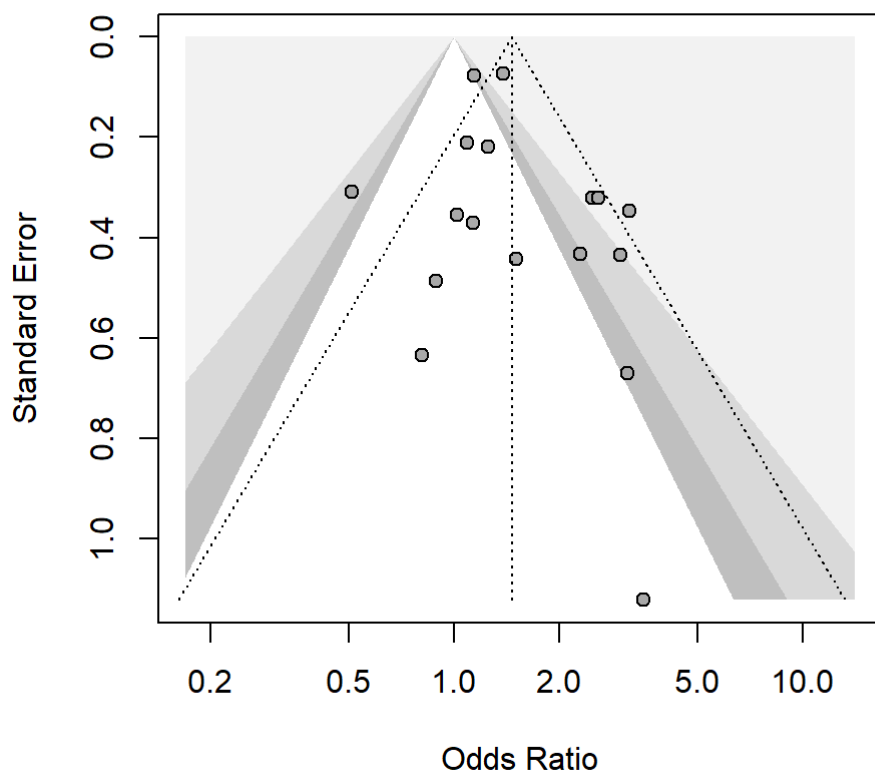


Table S1. Study characteristics

Title	Study pop.	Control pop.	Exposition	Staging
Changes in gynecologic and breast cancer diagnoses during the first wave of the COVID-19 pandemic: analysis from a tertiary academic gynecologic center in Germany (1)	patients diagnosed with gynecologic or breast cancer between January and June 2020 N= 236	Same pop. in 2019 N= 261	COVID 19	TNM
The impact of COVID-19 pandemic on the rate of newly diagnosed gynecological and breast cancers: a tertiary center perspective (2)	patients diagnosed with gynecological or breast cancer from March 2020 to April 2020 and November to December 2020 N= 371	Same periods in 2019 N= 240	COVID 19	TNM/ FIGO Stages
Has the COVID-19 Pandemic Caused Upshifting in Colorectal Cancer Stage? (3)	patients diagnosed with colorectal cancer for the first time from January to June 2020. N= 715	Same period from 2017 to 2019 N= 2514	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
COVID-19 is Affecting the Presentation and Treatment of Melanoma Patients in the Northeastern United States (4)	patients undergoing surgical management for a primary diagnosis of cutaneous melanoma from May 2020-December 2020 N= 313	Same pop. from August 2019 to March 2020 N= 375	COVID 19	Stage
Impact of the COVID-19 pandemic on breast and cervical cancer stage at diagnosis in Brazil (5)	Patients with histologically confirmed breast or cervical carcinoma of any histologic type.from from 1 September 2020 to 31 January 2021 N= 312	Same pop. from from 1 September 2019 to 31 January 2020 N= 517	COVID 19	Stages

Title	Study pop.	Control pop.	Exposition	Staging
The impact of the COVID-19 pandemic on oncological disease extent at FDG PET/CT staging: the ONCOVIPET study (6)	Only patients ≥ 18 years of age with a cancer diagnosis and FDG-avid tumours, who performed a whole-body PET/CT for staging purposes for Lung, Gynecologic, Gastrointestinal, lymphoma, breast, head and neck, myeloma, melanoma from June 1 to October 31, 2020. N=371	Same pop. from June 1 to October 31, 2019 N= 240	Covid 19	TNM
Gastrointestinal Cancer Stage at Diagnosis Before and During the COVID-19 Pandemic in Japan (7)	Patients who were diagnosed with gastrointestinal cancer from March 2020 to December 2020 N=949	Same pop. from January 2017 to February 2020 N= 4218	COVID 19	Stages

Title	Study pop.	Control pop.	Exposition	Staging
Significant Decrease in Annual Cancer Diagnoses in Spain during the COVID-19 Pandemic: A Real-Data Study (8)	All patients diagnosed between 13 March 2020 and 13 March 2021 for 24 cancer types (cf study) N= 2340	Same pop from between 13 March 2019 and 13 March 2020 N= 2825	COVID 19	Stages
Head and Neck Cancer During Covid-19 Pandemic: Was there a Diagnostic Delay? (9)	Patients with newly diagnosed laryngeal, salivary, skin of the head and neck, nasal, paranasal, oral, pharyngeal and occult cancer from from March 1st, 2020 to October 15th, 2020. N= 125	Same pop. from from March 1st, 2019 to October 15th, 2019. N= 139	Covid 19	Stages
How Do Breast Cancer Patients Present Following COVID-19 Early Peak in a Breast Cancer Center in Turkey? (10)	New patients diagnosed for breast cancer between May and June 2020 N= 36	Same pop. from May and June 2017-2019 N= 42	COVID 19	Notion of Early/ Advanced or Metastatic disease.

Title	Study pop.	Control pop.	Exposition	Staging
Impact of the COVID-19 pandemic on the diagnosis and treatment of men with prostate cancer (11)	all patients in England newly diagnosed with prostate cancer between between March, 23 and December, 31 2020 N= 15360	Same pop. during same period in 2019 N= 23715	COVID 19	Stage
Study of the gastrointestinal tumor progression during the COVID-19 epidemic in Wuhan (12)	Patients with gastro intestinal tumor admitted in Wuhan Union Hospital from March To April 2020 N= 137	Same pop. in same period in 2019. N= 351	COVID 19	pTNM
Time to Treatment Initiation for Breast Cancer During the 2020 COVID-19 Pandemic (13)	New histologic diagnosis of invasive breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS) between January 1, 2020, and May 15, 2020 N= 162	Same pop. between 01/01/2018 and 15/05/2018 N= 198	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
Advanced Stages and Increased Need for Adjuvant Treatments in Breast Cancer Patients: The Effect of the One-year COVID-19 Pandemic (14)	All patients with a diagnosis of breast cancer from February, 21, 2020 to February, 21 2021 N= 203	Same pop. from February, 21, 2019, to February, 20, 2020 N= 174	COVID 19	TNM
Impact of the first surge of the COVID-19 pandemic on a tertiary referral centre for kidney cancer (15)	Patients underwent renal surgery, from 18 March 2020 until 30 September 2020. N= 104	Same pop. from April 2019 to March 2020 N= 247	COVID 19	cTNM/ pTNM
Prostate Cancer Diagnosis and Management During One Year of the COVID-19 Pandemic (16)	Men with Pca between March 2020 and March 2021 N= 98	Same population between March 2019 and 2020 N= 187	COVID 19	ISUP
Digestive Oncology in the COVID-19 Pandemic Era (17)	patients with an inaugural digestive cancer diagnosis from March to August 2020 N= 91	Same pop. same period In 2018 N= 128	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
The impact of national non-pharmaceutical interventions ('lockdowns') on the presentation of cancer patients (18)	patients newly diagnosed with cancer in the South East London Cancer Alliance from April 2020 to September 2020. For lung, prostate, colorectal and breast cancer. N= 559	Same pop. from March 2020 to April 2020 N= 1038	COVID 19	Notions of Early and Late disease
Analysis of Early Impact of COVID-19 on Presentation and Management of Oral Cancers - an Experience from a Tertiary Care Hospital in South India (19)	All patients primarily concerned with oral cancers and who underwent primary surgical management for oral cancers with a curative intend from April 2020 to June 2020 N= 26	Same pop. from April 2019 to March 2020 N= 192	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
Consequences of the COVID-19 Pandemic and Governmental Containment Policies on the Detection and Therapy of Oral Malignant Lesions-A Retrospective, Multicenter Cohort Study from Germany (20)	Patients with a histopathological confirmed diagnosis of oral cancer from March, 13, 2020- November 1 2020. N= 205	Same pop. in same periods in 2018 and 2019. N= 425	COVID 19	TNM
The impact of the COVID-19 pandemic on the short-term survival of patients with cancer in Northern Portugal (21)	Cases of invasive tumors of the esophagus, skin melanoma, pancreas and prostate diagnosed between 2 March and 1 July 2020 N= 689	Same pop. in same period in 2019. N= 1264	COVID 19	Stage
Delay in Breast Cancer Treatments During the First COVID-19 Lockdown. A Multicentric Analysis of 432 Patients (22)	Patients with breast surgery from March 11, 2020 to May 30, 2020. N= 37	Same pop. in same period from March 11, 2019 to May 30, 2019 N= 46	COVID 19	TNM/ Grade

Title	Study pop.	Control pop.	Exposition	Staging
Impact of COVID-19 on presentation, staging, and treatment of head and neck mucosal squamous cell carcinoma (23)	new patients who presented to the head and neck surgical oncology clinic of Vanderbilt in Nashville from March to July 2020 N= 134	Same pop. in same period in 2019. N= 134	COVID 19	cTNM/ pTNM
The Impact of COVID-19 on the Diagnosis and Treatment of Lung Cancer at a Canadian Academic Center: A Retrospective Chart Review (24)	patient diagnosed with lung cancer between 1 March 2020 and 28 February 2021 N= 103	Same pop. between 1 March 2019 and 29 February 2020. N= 130	COVID 19	Notion of Early / Locoregional and Advanced disease
Reduction in healthcare services during the COVID-19 pandemic: Patient screening based on symptoms is an effective strategy for avoiding delayed laryngeal cancer diagnosis (25)	new histological diagnosis of laryngeal SCC from March 2020 to December 2020. N= 19	Same pop. from March 2019 to December 2019. N= 25	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
The "collateral damage" of the war on COVID-19: impact of the pandemic on the care of epithelial ovarian cancer (26)	Patient with EOC diagnosed and treated between 1st January 2020 and 31st December 2020. N= 39	Same pop. between 1st January 2019 and 30th September 2019. N= 43	COVID 19	Stage
Newly diagnosed cancer and the COVID-19 pandemic: tumour stage migration and higher early mortality (27)	newly referred patients with cancer from March to December 2020. Cancer: breast, CRC, NSCLC, melanoma, cervix. N= 383	Same pop. in same period in 2019. N= 539	COVID 19	Stage
Lung cancer stage distribution from before COVID-19 through 18 months of the pandemic: the experience of a large-volume oncological referral centre (28)	Patients with lung cancer analyzed by pathological staging review by a multidisciplinary tumour board from January to July 2020 and 2021 N= 255	Same pop. from January to July 2019. N= 122	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
COVID-19 pandemic impact on uro-oncological disease outcomes at an Italian tertiary referral center (29)	Patients treated for suspected or confirmed urologic cancer between January and December 2020. N= 186	Same pop. between January and December 2019. N= 207	COVID 19	cTNM
Impact of the Coronavirus Disease-2019 Pandemic on Pancreaticobiliary Disease Detection and Treatment (30)	Newly diagnosed pancreaticobiliary cancer from 7 April to 25 May 2020 AND 26 May to 31 July. N= 43	Same pop. from 1 April 2018 to 6 April 2020. N= 144	COVID 19	Stages
Impact of Coronavirus Disease 2019 on Clinical Characteristics in Patients With Lung Cancer: A Large Single-Centre Retrospective Study (31)	patients with lung cancer in Mianyang Central Hospital from February to July 2020. N= 231	Same pop. from February to July 2019. N= 156	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
Thyroid surgery during coronavirus-19 pandemic phases I, II and III: lessons learned in China, South Korea, Iran and Italy (32)	Patients treated at the Division of Thyroid Surgery of the China-Japan Union Hospital of Jilin University from January 25 to April 20, 2020 N= 328	Same pop. from January 25 to April 20, 2019. N= 731	COVID 19	TNM
Pattern of breast cancer presentation during the COVID-19 pandemic: results from a cohort study in the UK (33)	all new breast cancer diagnoses from May to October 2020. N= 163	Same pop. from May to October 2019. N= 276	COVID 19	Stage
Head and neck surgery during the coronavirus-19 pandemic: The University of California San Francisco experience (34)	patients undergoing head and neck or reconstructive surgery between March 16, 2020 and April 16, 2020. N= 22	Same pop. between March 16, 2019 and April 16, 2019. N= 30	COVID 19	Stage
Delayed Breast Cancer Detection in an Asian Country (Taiwan) with Low COVID-19 Incidence (35)	All patients receiving a breast biopsy between January 21 and July 31, 2020. N= 115	Same pop Between January 21 and July 31, 2019. N= 128	COVID 19	Invasive VS Non Invasive

Title	Study pop.	Control pop.	Exposition	Staging
Two-month stop in mammographic screening significantly impacts on breast cancer stage at diagnosis and upfront treatment in the COVID era (36)	women diagnosed with BC in the province of Modena between May 2020 and July 2020. N= 164	Same pop. between May and June 2019. N= 183	COVID 19	Stage
Diagnostic pathway and stage migration of sinonasal malignancies in the era of the COVID-19 pandemic (37)	patients treated for sinonasal malignancies between January 2020 and December 2020. N= 19	Same pop between January 2018 and December 2019. N= 30	COVID 19	cTNM/ Stage
Impact of the COVID-19 pandemic on diagnosis, stage, and initial treatment of breast cancer in the Netherlands: a population-based study (38)	Women older than 18 years and diagnosed with breast cancer during weeks 2–17 of 2020. N= 4769	Same pop. during Weeks 2-17 of 2018 and 2019. N= 11502	COVID 19	Stage
The Impact of the COVID-19 Pandemic on Breast Cancer Patients (39)	patients with invasive breast cancer treated between March 2020 and March 2021. N= 176	Same pop. between between March 2019 and March 2020. N= 206	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
Impact of the coronavirus disease 2019 pandemic on first-visit patients with oesophageal cancer in the first infection wave in Saitama prefecture near Tokyo: a single-centre retrospective study (40)	patients with new oesophageal cancer who first visited our hospital from April 2020 to March 2021. N= 168	Same pop. from April 2018 to March 2020. N= 378	COVID 19	cTNM
The impact of the COVID-19 pandemic on the management of head and neck cancer patients at a tertiary care institution in Poland (41)	all head and neck cancer patients who presented to the multidisciplinary tumour board (MTB) during the 12-month period from March 1, 2020 to February 28, 2021. N= 340	Same pop. from February 1, 2019 to February 28, 2020. N= 278	COVID 19	Locally Advanced, Regional, Advanced disease.
Characteristics and patterns of care of endometrial cancer before and during COVID-19 pandemic (42)	newly diagnosed EC treated in Italy from April 1, 2020 to March 31, 2021. N= 2446	Same pop. from March 1, 2019 to February 29, 2020. N= 2718	COVID 19	FIGO Stage

Title	Study pop.	Control pop.	Exposition	Staging
Impact of the COVID-19 Pandemic on Surgical Treatment Patterns for Colorectal Cancer in a Tertiary Medical Facility in Korea (43)	Patients with colon and rectal cancer who underwent surgery at the Asan Medical Center March to September 2020. N= 643	Same pop. from same period in 2019. N= 1413	COVID 19	Stage
Esophagectomy for Esophageal Cancer Performed During the Early Phase of the COVID-19 Pandemic (44)	all patients who underwent esophagectomy for esophageal cancer from March 1, 2020 to June 30, 2020. N= 32	Same pop. from January 1, 2019, to December 31, 2019. N= 67	COVID 19	Stage
Impact of two waves of Sars-Cov2 outbreak on the number, clinical presentation, care trajectories and survival of patients newly referred for a colorectal cancer: A French multicentric cohort study from a large group of University hospitals (45)	new CRC cases between 1 January 2020 and 31 December 2020. N= 176	Same pop. in Same period in 2018 and 2019. N= 413	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
Impact of the COVID-19 Pandemic on the Diagnosis and Surgery of Breast Cancer: A Multi-Institutional Study (46)	patients diagnosed with breast cancer from 1 February to 31 July 2020. N= 1023	Same pop in same period in 2019. N= 1044	COVID 19	Stage
Fewer head and neck cancer diagnoses and faster treatment initiation during COVID-19 in 2020: A nationwide population-based analysis (47)	all patients with a pathologically confirmed first primary head and neck malignancy from 1 June to 31 December 2020. N= 1641	Same pop. in same periods in 2018-2019. N= 3287	COVID 19	Stage
Cervical cancer and COVID-an assessment of the initial effect of the pandemic and subsequent projection of impact for women in England: A cohort study (48)	all cervical cancers between May and October 2020. N= 152	Same pop. between May and October 2019. N= 208	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
The effect of COVID-19 pandemic on laryngeal cancer in a tertiary referral center (49)	patients who operated due to laryngeal cancer in a tertiary referral hospital's ENT department, period not clear. N= 40	Same pop, period not clear. N= 57	COVID 19	cTNM
Care in the time of COVID-19: impact on the diagnosis and treatment of breast cancer in a large, integrated health care system (50)	patients with breast cancer diagnosed between March 17 and May 17, 2020. N= 247	Same pop. between March 17 and May 17, 2019. N= 703	COVID 19	cTNM/ Grade
Collateral effects of the coronavirus disease 2019 pandemic on lung cancer diagnosis in Korea (51)	patients, aged 18 years or older, who were diagnosed with pathological lung cancer between February and June 2020. N= 169	Same pop between February and June during 2017–2019. N= 443.	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
COVID-19 and the emergency presentation of colorectal cancer (52)	Patients with diagnosis of Colorectal adenocarcinoma in 2020. N= 267	Same pop. in 2018-2019. N= 539	COVID 19	pTNM
Impact of the Novel Coronavirus 2019 (COVID-19) Pandemic on Head and Neck Cancer Care (53)	Patients over 18 years of age who presented for head and neck oncologic care from March 18, 2020, to May 20, 2020. N= 117	Same pop. in same period in 2019. N= 69	COVID 19	cTNM
Did the COVID-19 lockdown result in a delay of colorectal cancer presentation and outcomes? A single centre review (54)	Initial and revised diagnosis between 7/4/20 and 7/10/20. N= 53	Same pop. between 6/10/19 and 6/4/20. N= 38	COVID 19	pTNM
What Has Changed During the COVID-19 Pandemic? - The Effect on an Academic Breast Department in Portugal (55)	Breast cancer patients between March 2020 and March 2021. N= 97	Same pop. same period one year previously. N= 162	COVID 19	Stage

Title	Study pop.	Control pop.	Exposition	Staging
The impact of COVID-19 on head and neck cancer diagnosis and disease extent (56)	Patients presenting with newly diagnosed or recurrent HNC from May 14, 2020 to June 18, 2020. N= 117	Same pop. in same period from from May 16, 2019 to June 20, 2019. N= 156	COVID 19	cTNM
Impact of the COVID-19 lockdown in France on the diagnosis and staging of breast cancers in a tertiary cancer centre (57)	patients who underwent an imaging-guided percutaneous breast biopsy performed from January to July 2020. N= 134	Same period in 2019. N= 120	Covid 19	TNM
A prospective cohort study of the safety of breast cancer surgery during COVID-19 pandemic in the West of Scotland (58)	People with surgical treatment for invasive or non-invasive breast cancer between 23 March 2020 and 15 May 2020. N= 168	Same pop. in 2015. N= 1390	COVID 19	cTNM/ pTNM/ Grade

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Table S2. Study quality assessment(124)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Kaltofen(125)	N	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Knoll(126)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Lim(127)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Davis(128)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Bonadio(129)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Caldarella(130)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Kuzuu(131)	Y	Y	Y	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Ruiz-Medina(132)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Lucidi(133)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Işıklar(134)	Y	Y	NR	N	N	N	UK	NA	Y	NA	Y	N	UK	N
Nossiter(135)	Y	Y	Y	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Cai(136)	Y	Y	Y	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Hawrot(137)	Y	Y	Y	N	N	N	UK	NA	Y	NA	Y	N	UK	N
Vanni(85)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Kuusk(138)	N	N	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Pepe(139)	N	N	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Brito(140)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	N	N	UK	N
Purushotham(141)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Riju(142)	N	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Heimes(143)	N	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Morais(144)	Y	Y	Y	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Vanni(86)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	N	N	UK	N
Stevens(145)	Y	Y	Y	Y	N	N	UK	NA	Y	NA	N	N	UK	N
Kasymjanova(146)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Murri(147)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Goenka(148)	N	Y	NR	N	N	N	UK	NA	Y	NA	Y	N	UK	N
Guven (149)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Bertolaccini(150)	Y	N	NR	NR	N	N	UK	NA	Y	NA	Y	N	UK	N
Oderda(151)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Ikemura(152)	N	N	NR	NR	N	N	UK	NA	Y	NA	CD	N	UK	N
Zhang(153)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Zhang(154)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Borsky(155)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Wai(156)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Chou(157)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	CD	N	UK	N
Toss(158)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Meerwein(159)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	Y
Eijkelboom(84)	Y	Y	Y	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
İlgün(160)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Miyawaki(161)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Szewczyk(162)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Bogani(163)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Choi(164)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Dolan(165)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Kempf(166)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Kang(167)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Schoonbeek(168)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Davies(169)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Elibol(170)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Tang(171)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Park(172)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Shinkwin(173)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Thompson(174)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Lee(175)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Simão(176)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Kiong(177)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Linck(178)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	Y	N	UK	N
Romics(179)	Y	Y	NR	Y	N	N	UK	NA	Y	NA	N	N	UK	N

Abbreviations: Y = Yes, N = No, UK = Unknown NA= Not Applicable NR= Not Reported CD= Can not Determined

Questions:

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible people at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)

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doi:10.10/X

Table S3: Synthesis of first national lockdowns and cancer screening disruptions

Country	Date of First National Lockdown	Cancer Screening Disruptions
Italy	09/03/2020 – 03/05/2020(13)	From March to May 2020(13)
Netherlands	from 15 March until early June 2020(14)	From March, 12, 2020 to mid May 2020(15)
Spain	14/03/2020 - 09/05/2020(16,17)	From 12/03/2020 to mid May 2020(18,19)
Turkey	29/04/2021 – 14/05/2021(20). No national lockdown in 2020.	From March 2020 to June, 1st 2020 (21)
USA	<p>Main lockdowns:</p> <ul style="list-style-type: none"> • California: 19/03/2020 – 15/06/2021(22) • Connecticut: 23/03/2020 – 22/04/2020(23,24) • Illinois: 21/03/2020 – 30/05/2020(25) • Kansas: 24/03/2020 – 19/04/2020(26) • Massachusetts: 24/03/2020 – 04/05/2020(27) • Michigan: 24/03/2020 – 13/04/2020(28) • New York: 22/03/2020 – 13/06/2020(29) • Oregon: 24/03/2020 – 15/05/2020(30) • Wisconsin: 24/03/2020 – 13/05/2020(31) 	Mid March to Mid July 2020(32)
Taiwan	No national lockdown(33)	No cancer screenings suspension(34)
Switzerland	17/03/2020 – 27/04/2020(35)	From mid March 2020 to 6 weeks later(36)
Germany	22/03/2020 – 20/04/2020(37)	From late March to late April 2020(38)
Portugal	18/03/2020 – 02/05/2020(39)	From mid March to May 2020(39)
China	<p>Main provinces(40):</p> <ul style="list-style-type: none"> • Hubei: 23/01/2020 - 25/03/2020 • Zhejiang: 02/02/2020 – 20/02/2020 • Xinjiang: 18/07/2020 – 26/08/2020 • Hebei: 07/01/2021 – 31/01/2021 • Shaanxi: 22/12/2021 – 16/01/2022 • Henan: 10/01/2022 – 03/02/2022 • Guangdong: 14/03/2022 – 21/03/2022 • Shanghai: 01/04/2022 – 01/06/2022 	No clear national datas
France	17/03/2020 – 11/05/2020(41)	From mid March to 15/06/2020(42)
Canada	<p>Main provinces:</p> <ul style="list-style-type: none"> • Ontario: 17/03/2020 – 14/05/2020(43) 	23/03/2020 – 26/05/2020(24)

	<ul style="list-style-type: none"> • British Columbia: 18/03/2020 – 18/05/2020(44) • Quebec: 18/03/2020 – 05/04/2020(45) 	
United Kingdom	23/03/2020 – 10/05/2020(46)	Between March and April 2020(47)
South Korea	No national lockdown(48)	No cancer screening suspension(49)
Japan	No national lockdown(50)	From April 7 to May 25 2020(51)
Brazil	No national lockdown(52,53)	No population-based cancer screening programs in Brazil(53)
Singapore	07/04/2020 – 01/06/2020(54,55)	07/04/2020 – 01/06/2020(56)
Poland	13/03/2023-19/04/2020(57,58)	April-May 2020(59)
India	25/03/2020-08/06/2020(60,61)	During 2020 Lockdown(62)

Appendix S1. Pubmed and EMBASE search equations

Adapted from PubMed's 'Cancer filter', discontinued in 2019 ¹

#1

neoplasms OR American Cancer Society OR angiogenesis inducing agents OR antibodies, neoplasm OR antigens, neoplasm OR antineoplastic agents OR antineoplastic protocols OR biomarkers, tumor OR biopsy OR biopsy OR bone marrow purging OR bone marrow transplantation OR cancer care facilities OR cancer vaccines OR carcinogenicity tests OR carcinogens OR chemoembolization, therapeutic OR clonal evolution OR clonal evolution OR colonography, computed tomographic OR colonoscopy OR colposcopy OR combined modality therapy OR cryosurgery OR cytapheresis OR dna, neoplasm OR drug resistance, neoplasm OR drug screening assays, antitumor OR early detection of cancer OR gene expression regulation, neoplastic OR genes, neoplasm OR graft vs tumor effect OR hematopoietic stem cell transplantation OR hematopoietic stem cell mobilization OR immunotherapy, adoptive OR lymph node excision OR tumor-infiltrating OR mammography OR mastectomy OR medical oncology OR metastasectomy OR mohs surgery OR neoplasm grading OR neoplasm proteins OR neoplasm staging OR neoplasm transplantation OR neoplastic processes OR neoplastic stem cells OR oncogene fusion OR oncogenic viruses OR oncology nursing OR oncology service, hospital OR oncolytic viruses OR papanicolaou test OR papillomavirus vaccines OR peripheral blood stem cell transplantation OR polyomavirus OR radiotherapy OR radiotherapy planning, computer assisted OR rna, neoplasm OR second-look surgery OR SEER program OR stem cell transplantation OR transplantation conditioning OR tumor cells, cultured OR tumor escape OR tumor lysis syndrome OR tumor necrosis factors OR receptors, tumor necrosis factor OR tumor necrosis factor receptor-associated peptides and proteins OR ultrasonography, mammary OR AACR OR AJCC OR (ASCO NOT fungi) OR IARC OR "National Cancer Institute (U.S.)" OR UICC OR aCML OR AGCUS OR AILD OR AML OR ANLL OR ASCUS OR ATLL OR BRCA OR BRCA1 OR BRCA2 OR CIN OR CLL OR CMML OR CMPD OR ECCL OR EGIST OR FMTC OR GLNH OR HNPCC OR HNSCC OR HPV OR HSIL OR ICD O OR JCML OR JMML OR LGLL OR MGUS OR MLH1 OR MPD OR MSH2 OR NSCLC OR RAEB OR RCMD OR SCLC OR VOD OR 5q syndrome OR BCR ABL OR c erbB 2 OR c erbB2 OR carney complex OR cone biopsy OR denys drash OR estrogen receptor negative OR estrogen receptor positive OR li fraumeni OR meigs syndrome OR molar pregnancy OR peutz jehgers OR sentinel lymph node OR struma ovarii OR sturge weber OR zollinger ellison OR (aberrant AND crypt AND foci) OR ((anti-n-methyl-d-aspartate OR anti-nmda) AND encephalitis) OR (barrett AND

¹ https://www.nlm.nih.gov/bsd/pubmed_subsets/cancer_strategy.html, consulted on 24 May 2023

esophagus) OR (gestational AND trophoblastic) OR (microsatellite AND instability) OR (paget AND (breast OR nipple)) OR (polycythemia AND vera) OR (radiation AND therapy) OR (WAGR AND syndrome) OR (pap AND (smear OR smears)) OR cervical smear OR cervical smears OR pap test OR pap tests OR (PSA AND prostate) OR PSA test OR PSA testing OR (prostate AND specific AND antigen) OR acanthoma OR acanthomas OR acrochordon OR acrochordons OR acrospiroma OR acrospiromas OR adamantinoma OR adamantinomas OR adenoacanthoma OR adenoacanthomas OR adenoameloblastoma OR adenoameloblastomas OR adenocanthoma OR adenocanthomas OR adenocarcinoma OR adenocarcinomas OR adenofibroma OR adenofibromas OR adenolipoma OR adenolipomas OR adenolymphoma OR adenolymphomas OR adenoma OR adenomas OR adenomatosis OR adenomatous OR adenomyoepithelioma OR adenomyoepitheliomas OR adenomyoma OR adenomyomas OR adenosarcoma OR adenosarcomas OR adenosis OR aesthesioneuroblastoma OR aesthesioneuroblastomas OR ameloblastoma OR ameloblastomas OR amyloidoses OR anaplasia OR androblastoma OR androblastomas OR angioblastoma OR angioblastomas OR angioendothelioma OR angioendotheliomas OR angioendotheliomatosis OR angiofibroma OR angiofibromas OR angiofibrosarcoma OR angiogenesis factor OR angiokeratoma OR angiokeratomas OR angioleiomyoma OR angioleiomyomas OR angioliipoma OR angioliipomas OR angioma OR angiomas OR angiomatosis OR angiomyolipoma OR angiomyolipomas OR angiomyoma OR angiomyomas OR angiomyxoma OR angiomyxomas OR angioreticuloma OR angioreticulomas OR angiosarcoma OR angiosarcomas OR anticancer OR anticarcinogenesis OR anticarcinogenic OR antimutagenesis OR antineoplastic OR antioncogene OR antioncogenes OR antitumor OR antitumors OR antitumour OR antitumours OR apudoma OR apudomas OR argentaffinoma OR argentaffinomas OR arrhenoblastoma OR arrhenoblastomas OR astroblastoma OR astroblastomas OR astrocytoma OR astrocytomas OR astroglioma OR astrogliomas OR atypia OR baltoma OR basiloma OR basilomas OR biochemotherapies OR biochemotherapy OR bioradiotherapy OR Birt-Hogg-Dube OR blastoma OR blastomas OR Buschke-Lowenstein OR cachexia OR cancer OR cancerous OR cancers OR carcinogen OR carcinogenesis OR carcinogenic OR carcinogens OR carcinoid OR carcinoma OR carcinomas OR carcinomatosis OR carcinosarcoma OR carcinosarcomas OR cavernoma OR cavernomas OR cementoma OR cementomas OR cerbB2 OR ceruminoma OR ceruminomas OR chemodectoma OR chemodectomas OR chemoimmunoradiotherapy OR chemoimmunotherapies OR chemoimmunotherapy OR chemoprevention OR chemoradiation OR chemoradiotherapies OR chemoradiotherapy OR cherubism OR chloroma OR chloromas OR cholangiocarcinoma OR cholangiocarcinomas OR cholangiohepatoma OR cholangioma OR cholangiomas OR cholangiosarcoma OR cholesteatoma OR cholesteatomas OR chondroblastoma OR chondroblastomas OR chondroma OR chondromas OR chondrosarcoma OR chondrosarcomas OR chordoma OR chordomas OR chorioadenoma OR chorioadenomas OR chorioangioma OR chorioangiomas OR choriocarcinoma OR choriocarcinomas OR chorioepithelioma OR chorioepitheliomas OR chorionepithelioma OR chorionepitheliomas OR choristoma OR choristomas OR chromaffinoma OR chromaffinomas OR cocarcinogenesis OR collagenoma OR collagenomas OR colonoscopies OR coloscopy OR coloscopies OR comedocarcinoma

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#2

Neoplasm Staging[MeSH Terms] OR Neoplasm Metastasis[MeSH Terms] OR (stage[Title/Abstract] OR metasta*[Title/Abstract] OR pTNM[Title/Abstract] OR TNM[Title/Abstract])

#3

LitCGeneral[sb]

#4

Address OR Autobiography OR Biography OR Clinical Trial, Veterinary OR Dictionary OR Directory OR Duplicate Publication OR Expression of Concern OR Festschrift OR Historical Article OR Interactive Tutorial OR Interview OR Lecture OR Legal Case OR Legislation OR News OR Newspaper Article OR Observational Study, Veterinary OR Patient Education Handout OR Periodical Index OR Personal Narrative OR Portrait OR Preprint OR Published Erratum OR Randomized Controlled Trial, Veterinary OR Retracted Publication OR Retraction of Publication OR Scientific Integrity Review OR Technical Report OR Video-Audio Media OR Webcast

#5

"animals"[mh:noexp]

((#1 AND #2) AND #3) NOT #4 NOT #5

Appendix S2. Inclusion and exclusion criteria for article selection

Inclusion criteria:

- Studies published between January 2020 and April 2022 in PubMed or Embase
- English language only
- Patients >18 years old only
- Solid tumors only
- New cancer diagnosis
- Articles comparing stages before and after the outbreak of the Sars-Cov-2 pandemic

Exclusion criteria:

- Abstracts
- Posters
- Letters to the editor
- Guidelines
- Systematic reviews and other types of literature reviews
- Short communications
- Articles unpublished or from grey literature
- Articles with no or insufficient cancer staging information
- Articles focusing only on pre or post Sars-Cov-2 results (e.g., cross-sectional studies of cancer staging during the pandemic)
- Articles that only included metastatic patients

Appendix S3. List of data elements we extracted from included articles

1. Identification of articles:

- First author
- Titles
- PMID

2. Method-related items

- Country
- Study type
- Type of data collection (Cancer register, care records, other types)
- Mono or multicentric status
- Type of care center (primary, secondary or tertiary)
- Inclusion criteria
- Cancer type
- Period of interest
- Comparative period
- Notion of cancer screening postponement
- Notion of national lockdown
- Primary outcome
- Secondary outcomes

3. Result-related items

- Number of patients included for each period.
- Median or mean age for each period
- % of male patients for each period
- Time between diagnosis and treatment for each period
- Cancer staging for each period

Appendix S4. Classification of primary cancer types

- Breast cancer
- Colorectal cancer
- Other gastro: Esophageal, gastric, pancreatic, biliary tract, liver.
- Gynecologic cancer: Cervix, endometre, ovaries, vulvar/vagina.
- Genito-urinary: Kidney, bladder
- Other cancer: Head and neck (sinonasal, oral, thyroid), sarcoma, germ cells, CUP, mesothelioma.
- Melanoma
- Prostate
- Lungs

Impact de la crise COVID 19 sur la présentation clinique initiale des cancers solides nouvellement diagnostiqués : Une revue systématique de la littérature et une méta-analyse.

Contexte : Les perturbations de soins causées par la crise COVID 19 ont pu impacter la présentation initiale des cancers solides nouvellement diagnostiqués sur cette période ainsi que leur pronostic. Le but de cette revue systématique de la littérature était de comparer la distribution globale des stades des cancers solides avant et après les premières vagues de la pandémie.

Méthode : Une revue systématique de la littérature a été réalisée en suivant les recommandations PRISMA et MOOSE, par deux investigateurs indépendants au travers des publications disponibles sur MEDLINE et EMBASE. Une méta-analyse a été conduite afin de comparer le taux de métastases au diagnostic de cancers solides avant et après les premières vagues de la pandémie. Des analyses en sous-groupes ont été menées par type de cancer, et par localisation géographique de l'étude. L'hétérogénéité entre les études et les différences entre sous-groupes ont été vérifiées par des tests I^2 et X^2 .

Résultats : Des 2013 articles extraits par l'équation de recherche, 58 ont été inclus dans l'analyse finale, représentant 109 996 patients. Le taux de présentation métastatique au diagnostic était significativement plus important après les premières vagues de la pandémie (pooled OR: 1.29 (95% CI, 1.06-1.57), I^2 : 89% (95% CI, 86-91)). Les analyses en sous groupes par type de cancer ont révélé significativement plus de métastases au diagnostic pour les cancers du sein et les cancers gynécologiques (OR: 1.51 (95% CI 1.07-2.12) et OR: 1.51 (95% CI 1.04-2.18) respectivement). Les autres types de cancers ne révélaient pas de modifications significatives. Les analyses en sous groupes par localisation géographique des études montraient significativement plus de métastases au diagnostic en Italie (OR (95% CI) : 1.55 (1.01-2.39)) et en Espagne (OR (95% CI) : 1.14 (1.02-1.29)). Au contraire, moins de métastases au diagnostic ont été notifiées à Taiwan (OR (95% CI) : 0.51 (0.28-0.93)) et au Canada (OR (95%CI) : 0.14 (0.07-0.29)). La répartition des stades I-II VS III-IV et I-II VS III ne montrait quand à elle pas de différence notable par pays ou par type de cancer.

Conclusion : Malgré une hétérogénéité importante entre les études, notre méta-analyse a démontré un taux plus important de métastases au diagnostic après la pandémie COVID 19. La mise en place de mesures préventives de distanciation et le report des soins peuvent contribuer à expliquer ce résultats.

Spécialité :

[\[Médecine Interne et Immunologie Clinique\]](#)

Mots clés français :

[COVID 19](#), [Système de santé](#), [Détection précoce des cancers](#), [Recherche sur les système de soins](#), [Métastases](#), [Stadification des cancers](#).

Forme ou Genre :

[fMeSH : Dissertation universitaire](#)

[Rameau : Thèses et écrits académiques](#)