










Discordance of COVID-19 guidelines for patients with cancer: A systematic review

Pankaj Kumar Garg MCh¹  | Pallvi Kaul MS¹  | Deepti Choudhary MS²  |
Kiran Kalyan Turaga MD³  | Mahendra Pal Singh MCh¹  |
Ajeet Ramamani Tiwari MCh¹  | Vipin Arora MS⁴  | Nishant Agrawal MD⁵ |
Beat Rau MBA⁶  | Sai Yendamuri MD⁷ 

¹Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

²Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

³Section of Surgery and Surgical Oncology, Department of Surgery, The University of Chicago Medicine, Chicago, Illinois

⁴Department of ENT and Head Neck Surgery, University College of Medical Sciences and Guru Teg Bahadur Hospital, University of Delhi, Delhi, India

⁵Section of Otolaryngology-Head and Neck Surgery, Department of Surgery, The University of Chicago Medicine, Chicago, Chicago, Illinois

⁶Department of Surgery, Campus Virchow-Klinikum, Charité-Universitätsmedizin, Berlin, Germany

⁷Department of Thoracic Surgery, Roswell Park Cancer Institute, Buffalo, New York

Correspondence

Pankaj K. Garg, MS, DNB, MCh (Surgical Oncology), FUICC, FACS, FRCS (Glasg), Additional Professor, Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand 249203, India.
Email: dr.pankajgarg@gmail.com

Abstract

This review was aimed to systematically evaluate the available literature on the impact of COVID-19 on cancer care and to critically analyze the diagnostic and therapeutic strategies suggested by various healthcare providers, societies, and institutions. Majority guidelines for various types of cancers favored a delay in treatment or a nonsurgical approach wherever feasible. These guidelines are based on a low level of evidence and have significant discordance for the role and timing of surgery, especially in early tumors.

KEYWORDS

cancer, coronavirus, COVID-19, pandemic, SARS-CoV-2

1 | INTRODUCTION

The novel coronavirus disease (COVID-19) caused by SARS-CoV-2 originated in Wuhan, China where the first case was reported on 31st December 2019.¹ Within a short period, the World Health Organization (WHO) declared it as a Public Health Emergency of International Concern on 30th January 2020 and as a global pandemic on 11th March 2020.² This has led to significant concerns regarding the management of cancer patients. On one hand, patients with cancer are faced with a potentially fatal disease, risk of progression and being unresectable/untreatable, and risk of emergent complications if not treated on time.^{3,4} On the other, cancer patients are considered more vulnerable, with suggestions

for increased risk of developing severe infections and complications with poor prognosis and outcomes.⁴⁻⁶

As a response to this pandemic, several organizations have proposed guidelines in the management of cancer patients. In the field of oncology, clinical practice guidelines (CPGs) and consensus statements form a backbone in decision-making and have consistently shown a positive impact on clinical practice and outcomes.⁷ Guidelines can be extremely helpful in the setting of limited evidence, but varied discordant guidelines can be confusing to individuals, physicians, and healthcare systems. If not updated appropriately, they can lead to harm and moral distress. The purpose of this review was to summarize and analyze the guidelines proposed in the literature for patients with cancer during the COVID crisis.

2 | METHODS

2.1 | Search strategy

A comprehensive search strategy was developed following a consensus among the co-authors in collaboration with an external expert. The search strategy used variations in keywords—coronavirus, COVID, and cancer—to retrieve articles. Three electronic databases—Medline (Pubmed), Embase, and Scopus—were searched from their inception to 2nd May 2020. Full text of the pertinent articles was obtained and evaluated. The references of these articles were manually searched to look for any relevant studies. EndNote, version 9 (Clarivate Analytics), was used to facilitate the search process. The review has been done in accordance with the PRISMA guidelines.

2.2 | Inclusion/exclusion criteria for the studies

Following criteria were used for studies to be suitable for inclusion in the systematic review:

1. Any study that has addressed the issue of cancer at the time of COVID-19 pandemic.
2. Title and abstract in the English language.

The exclusion criteria are:

1. Animal studies
2. Erratum/corrections

2.3 | Data extraction

Two authors (PKG and PK) searched the electronic databases and screened all the titles and abstracts from the selected articles. Any disagreement was resolved by consensus among the authors. The full texts of the selected articles were analyzed by the four authors (PK, PKG, MPS, and ART). The relevant information was extracted using a predefined data extraction sheet.

3 | RESULTS

3.1 | Literature review

The search strategy yielded 1699 articles. A total of 1133 articles were identified after removing the duplicates. After initial screening, full texts of 212 articles were assessed for inclusion in the systematic review (Figure 1).

Articles were classified under five categories based on tumor types (Figure 2A)—(a) Solid organ malignancies (n = 146), (b) hematological malignancies (n = 6), (c) radiation therapy related

(n = 8), (d) medical oncology/immunotherapy related (n = 5), and (e) miscellaneous (n = 47).

3.2 | Timeline of publications

There has been a progressively rising trend over the last 4 months. Of the total 212 publications analyzed in this review, the majority (n = 128, 60.3%) of them were published in April 2020.

3.3 | Types of publications

Based on the type of publications, the articles were categorized into five categories—guidelines/recommendations/review articles (n = 86, 40.5%), research article/survey (n = 25, 11.8%), case reports/series (n = 18, 8.5%), editorials (n = 25, 11.8%), and short communication/commentary/expert opinions (n = 58, 27.3%). Table 1 displays an overview of various types of publications in different domains of cancer.

3.4 | Country of origin

Based on the country of origin, majority of data originated from countries like the United States, China, and Italy, which were worst affected by this pandemic (Table S1).

3.5 | Different tumor types

3.5.1 | Solid organ malignancies

Majority of publications address the issue of COVID-19 in head and neck cancer patients (n = 46) followed by lung cancer (n = 32). Figure 2B displays the distribution of publications included in the current systematic review addressing various solid organ malignancies.

Head and neck cancers

Forty-six articles fulfilled our inclusion criteria, addressing the effect of COVID-19 on head and neck cancers. Table 2 summarizes a few relevant recommendations/guidelines by various expert groups and societies.⁸⁻¹¹ All the guidelines consider surgery in head and neck region as a procedure with high-risk for viral aerosolization and recommend personal protective equipment usage mandatory in COVID-19 positive patients and patients undergoing aerosol-generating procedures like a tracheostomy. There is a uniform consensus regarding maintaining endotracheal intubation for up to 21 days before considering a tracheostomy to reduce the viral load.⁹ Regarding the management of SARS-CoV-2 negative patients, there is discordance in the recommendations for treatment, especially for early stage

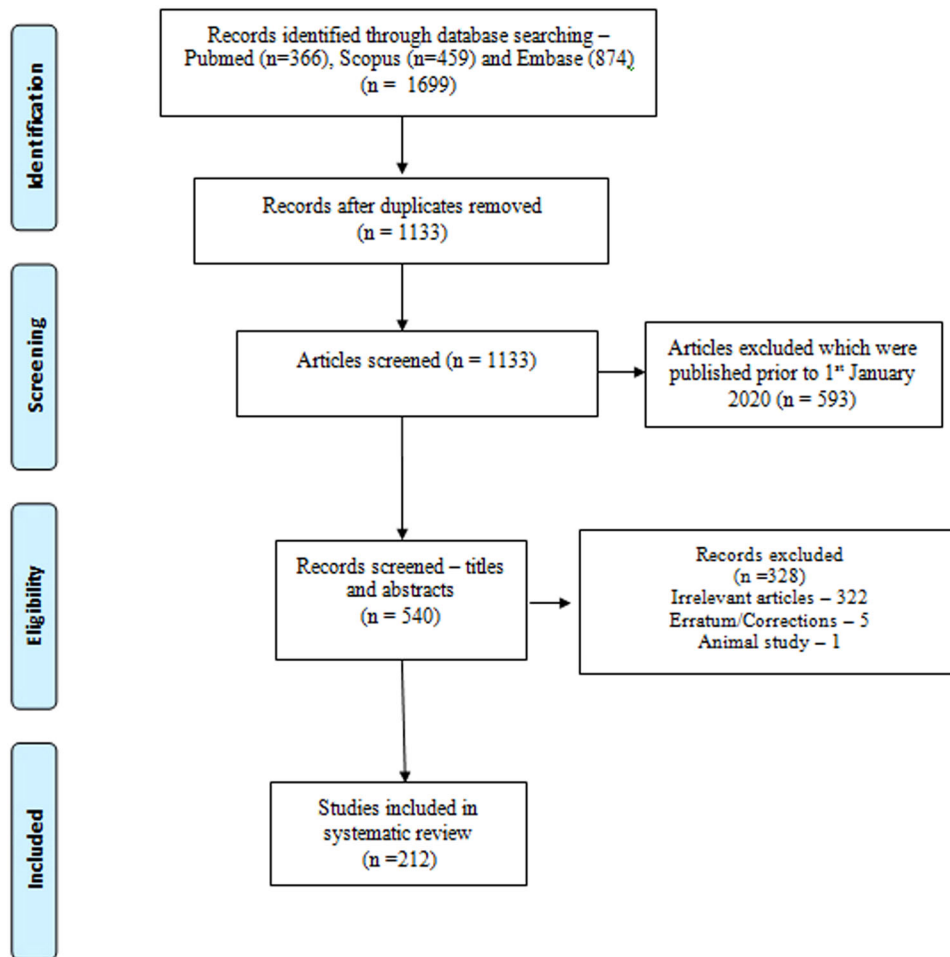


FIGURE 1 Flowchart of PRISMA [Color figure can be viewed at wileyonlinelibrary.com]

HNSCC. Chaves et al¹² recommend individualized treatment based on subsite for early cancers and are strictly against interrupting or postponing the treatment whereas Maniakas et al¹⁰ and Fakhry et al⁸ recommend short-term deferrals for surgery or

a nonsurgical treatment option, wherever feasible, in case of early cancers. There is also discordance in opinion regarding the use of NACT in advanced cases. While Chaves et al¹² do not recommend administering induction chemotherapy as an option to postpone

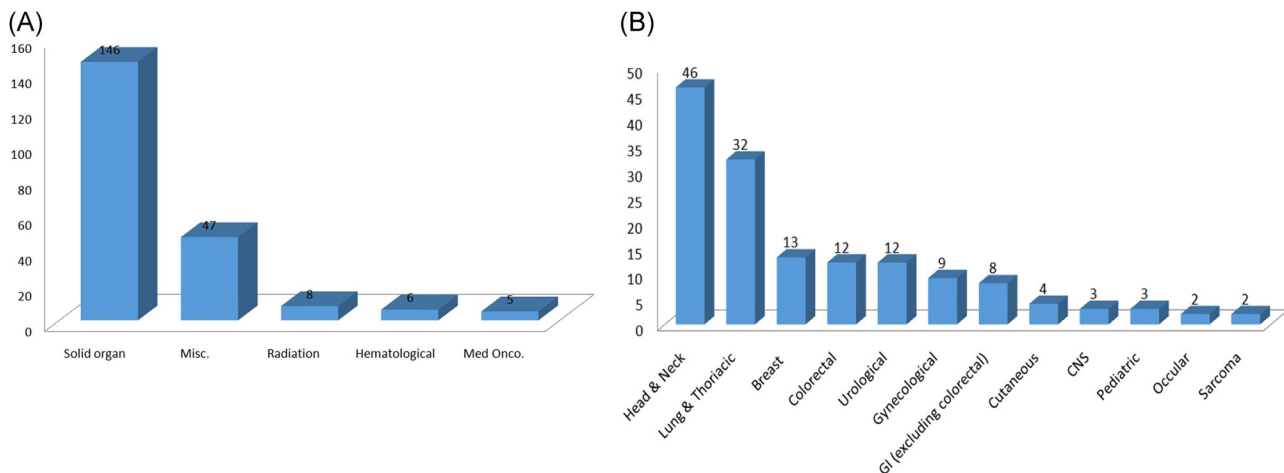


FIGURE 2 Bar-charts depicting the (A) number of publications in various domains of cancer and (B) distribution of publications as per the type of solid organ malignancy [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Various types of publications in the domain of cancer

Total number of publications for various types of cancers																	
Solid organ malignancies																	
Type of article	Breast	Colorectal	Cutaneous	GI cancers (excluding colorectal)	Gynecological tumors	Head and neck	Lung & Thoracic	CNS tumors	Ocular tumors	Pediatric tumors	Urological tumors	Sarcoma	Hematological	Radiation therapy related	Medical oncology/immunotherapy	Miscellaneous	Total
Guidelines/review articles/recommendation/expert group	8	6	1	7	6	15	14	1	1	0	1	0	3	7	1	15	86
Research article/survey	1	0	0	1	0	10	1	1	0	1	1	0	1	0	1	7	25
Case reports/series	1	1	0	0	2	2	10	0	0	0	0	0	2	0	0	0	18
Editorials	2	1	1	0	0	8	0	0	0	0	2	0	0	1	1	9	25
Short communication/commentary/expert opinion/news articles	1	4	2	0	1	11	7	1	1	2	8	2	0	0	2	16	58
Total	13	12	4	8	9	46	32	3	2	3	12	2	6	8	5	47	212

TABLE 2 Guidelines/recommendations for the treatment of head and neck cancers during COVID-19 pandemic

Expert groups	Recommendation
Fakhry et al ⁸ (French consensus statement)	<p>Surgery—3 groups of patients, based on the treatment timescale:</p> <ul style="list-style-type: none"> • Group A: life-threatening emergencies → immediate treatment. Screen if possible, in <24 hours else, consider as COVID positive and proceed with surgery. • Group B: cancers where postponing treatment beyond 1 month → negative prognostic impact <ol style="list-style-type: none"> a. Tracheostomy not required—Routine patient management preferably in single hospital stay. If not possible → refer b. Tracheostomy required—high contamination risk → postpone surgery or a nonsurgical alternative. • Group C: cancers where treatment can be postponed for 6 to 8 wk → reassess.
David et al ⁹ (University of California, Tracheostomy Guidelines)	<ol style="list-style-type: none"> 1) Personal protective equipment—mandatory in COVID-19 positive and asymptomatic patients undergoing aerosol generating procedures. 2) Viral load reduction—maintaining endotracheal intubation for 21 days prior to tracheostomy. 3) Preoperative testing—not done in asymptomatic 4) Indications and timing for tracheostomy in the COVID-19 positive or person under investigation (PUI) patient—proceed after MDT discussion. Poor survival (<20%) → defer. Ventilator parameters for safe tracheostomy placement → (PEEP) < 12 and (FiO₂) < 0.60. 5) Technical considerations during tracheostomy—preferentially performed in ICU, with minimum aid. Open or percutaneous procedure → based on patient factors and surgeon preference. During tracheal incision and endotracheal tube exchange, a systemic paralytic agent administered. Meticulous hemostatic technique. Close communication between surgical and anesthesia teams. Ventilation should be held prior to creation of the tracheal window and deflation of ETT cuff. Application of suction to the surgical wound during tube change. Suction circuit should include a high-efficiency particulate arrestance (HEPA). 6) Tracheostomy maintenance—performed with droplet-level precautions (gloves, gown, mask/eye protection) at a minimum. Closed-circuit suction, heat and moisture exchanger (HME) if not ventilated. Cuff inflation is preferred. The frequency of tracheostomy changes should be reduced to every 1-3 mo for all patients unless clinically urgent and avoided in COVID-19-positive patients.
Maniakas et al, MD Anderson Head and Neck Surgery Treatment Guidelines Consortium ¹⁰	<ol style="list-style-type: none"> (I) Subsite-specific triage system: <ol style="list-style-type: none"> (a) SARS-CoV-2 positive—no resection until life-threatening (b) SARS-CoV-2 negative—pass symptom screening and appropriate testing 1 day prior to intended surgery date (II) Disease subsites <ol style="list-style-type: none"> (a) Oral cavity (high risk for viral aerosolization) <ul style="list-style-type: none"> • Premalignant disease—defer, telemedicine visits • Early malignant disease—short-term deferral, telemedicine. Stable → monitor; surgery if progresses. • Intermediate malignant disease—primary surgery • Advanced malignant disease—NACT (b) Oropharynx (high risk for viral aerosolization) HPV-negative patients prioritized <ul style="list-style-type: none"> • Early disease—deferral/telemedicine visits, • Intermediate disease—deferral/telemedicine visits/nonsurgical treatment • Advanced disease—nonsurgical treatment (c) Larynx/hypopharynx (high risk for viral aerosolization). <ul style="list-style-type: none"> • Early disease—nonsurgical treatment/telemedicine visits • Intermediate disease—nonsurgical treatment • Advanced disease—nonsurgical treatment. Surgery → advanced cartilage invasion, extra-laryngeal spread, recurrent disease, or high risk for aspiration (d) Sinonasal and skull base (high risk for viral aerosolization) <ul style="list-style-type: none"> • Routine nasal endoscopy to be deferred. • Intermediate stage tumors -CTRT/RT alone • Advanced mucosal-derived malignancies <ol style="list-style-type: none"> (i) SNUC or SCC—NACT (ii) Sinonasal mucosal melanoma—neoadjuvant immunotherapy or targeted therapy (iii) Skull base sarcomas—RT (iv) Low grade and slow growing neuroendocrine carcinoma (NEC) and olfactory neuroblastoma (ONB)—Defer and monitor (v) Tumors of minor salivary gland origin—Defer and monitor unless rapidly growing (vi) High-grade NEC and Hyams Grade IV ONB—Consider NACT

(Continues)

TABLE 2 (Continued)

Expert groups	Recommendation
	<p>(e) Salivary Gland</p> <ul style="list-style-type: none"> • Low-Grade/slow growing intermediate grade—Defer with telemedicine visits. • Surgery → Pediatric population, high-grade malignancies. NACT prior to surgery • Endocrine • Early stage: postpone surgery • Intermediate stage: postpone most surgeries • Advanced stage: proceed with most surgeries (thyroid tumor requiring acute airway management)
Ranasinghe et al ¹¹ (The University of Pittsburgh approach for major head and neck reconstruction)	<p>Three tier system: (for prioritization of cancer surgery)</p> <ul style="list-style-type: none"> • Tier 1—Benign pathology, minor procedures + nonmelanoma skin cancer <2 cm • Tier 2—Low-grade malignancy, nonmelanoma skin cancer >2 cm, Diagnostic biopsy. • Tier 3—Mucosal SCC, DTC with local invasion, Poorly differentiated thyroid cancer, Melanoma, Direct laryngoscopy and biopsy. <p>(for prioritization of reconstructive head and neck surgery)</p> <ul style="list-style-type: none"> • Tier 1: Stage reconstruction with wound care, skin grafting, or local flap—Small oral cavity defect without neck communication, oroantral fistula, Facial nerve reanimation, Traumatic maxillofacial injuries • Tier 2: Consider free flap reconstruction, substitute loco-regional flaps if feasible—Maxillectomy defects, Lateral mandibular defects Tongue, FOM defects <50% without large neck communication RND with exposed great vessels, Large external skin defects with exposed vital structures • Tier 3: Free-flap reconstruction required—anterior oromandibular defects, Tongue, FOM defects >50% with neck communication, Total laryngo-pharyngectomy defects requiring tubed reconstruction, Skull-based defects with exposed intracranial structures/CSF leak. <p>Only tier 3 cases are moved forward with scheduling</p>
Chaves et al ⁹ (Multicentric- Emergency guidelines for HNSCC)	<ol style="list-style-type: none"> 1. SARS-CoV-2 negative patients→ not to postpone/interrupt treatment 2. Endoscopy to be done only if necessary. 3. Early Stage HNSCC→ individualize treatment-based on subsite 4. LAHNSCC→ CCRT with cisplatin remains the standard of care 5. Upfront surgery/radiotherapy not to be replaced by induction chemotherapy. 6. Recurrent/metastatic disease→ individualize whether to offer any treatment or not based on performance status. 7. Consider hypo-fractioned radiation therapy for palliative care. 8. Prefer virtual options over face-to-face visits.
Thomson et al (ASTRO-ESTRO consensus statement)	<ol style="list-style-type: none"> 1. Strong agreement: <ul style="list-style-type: none"> • Not to postpone initiation of HNSCC radiotherapy by 4-6 wk • Delay in initiation of RT till SARS-CoV-2 test is negative • High/very high priority to radical radiotherapy. • Continue use of concomitant chemotherapy. • Consider a hypofractionated radiation schedule. 2. Agreement: <ol style="list-style-type: none"> a) High priority→ PORT for involved margins. b) Low priority → PORT for minor risk factors. c) Not to alter standard radical radiation dose fractionation. d) (Chemo-)radiotherapy for locoregionally advanced HNSCC e) Early oral cavity→ consider waiting for surgery (maximum 8 wk) 3. No agreement: <ol style="list-style-type: none"> a) No treatment acceptable in certain cases of slow growing tumors.

upfront surgery and radiotherapy due to significant risk of immunosuppression and a high possibility of contracting COVID-19 infection, Maniakas et al¹⁰ recommend considering NACT for advanced malignant disease based on a case-by-case discussion keeping in mind the current pandemic situation. However, there is a uniform consensus among all the groups to avoid or limit the

number of face-to-face visits and consider virtual options like telemedicine.^{10,12} Regarding the role of radiation therapy in the management of HNSCC in the current pandemic, the American Society of Radiation Oncology (ASTRO) and European Society for Radiotherapy and Oncology (ESTRO)¹³ have issued a joint consensus statement, the salient features of which are listed in Table 2.

TABLE 3 Guidelines/recommendations for the treatment of lung neoplasms during COVID-19 pandemic

Expert groups	Recommendation
Banna et al ¹⁴	<p>Start the treatment when possible:</p> <p>Non-small cell lung cancer (NSCLC): NACT for locally advanced resectable disease, Sequential/concurrent CHT/RT for stage III disease, First-line treatment for metastatic disease, Palliative or ablative radiotherapy (SBRT) outside the lung.</p> <p>Small cell lung cancer (SCLC): First-line treatment for extensive-stage disease. Concurrent CHT/RT for limited-stage disease, Palliative or ablative radiotherapy (SBRT) outside the lung.</p> <p>Do not stop the treatment without justification:</p> <p>NSCLC: NACT for locally advanced resectable disease, Sequential/concurrent CHT/RT for stage III disease, first-line treatment for metastatic disease, maintenance ICI.</p> <p>SCLC: Concurrent CHT/RT for limited-stage disease, first-line treatment for metastatic disease.</p> <p>Prefer:</p> <p>NSCLC: CT/RT for stage III disease, oral chemotherapy for ECOG PS 2 and elderly patients (instead of intravenous).</p> <p>SCLC: Oral rather than intravenous chemotherapy.</p> <p>Withhold or delay after careful consideration:</p> <p>NSCLC: Withhold ACHT in patients at significant COVID-19-related risk, delay ICI (within 42 days) for stage III disease after CHT/RT, withhold maintenance pemetrexed, prolong intervals of ICI</p> <p>SCLC: Prolong intervals of ICI</p> <p>Do not start the treatment without justification</p> <p>NSCLC: Third and beyond lines of chemotherapy inpatients at significant COVID-19-related risk</p> <p>SCLC: PCI (favoring MRI surveillance), thoracic consolidation radiotherapy extensive stage, third and beyond lines of chemotherapy in patients at significant COVID-19-related risk.</p>
Cafarotti et al ¹⁵	<p>Risk stratification or lung cancer progression and COVID-19 infection</p> <p>Low risk of progression: T1 (a-c) N (0-1), T2 (a-b) N (0-1), T3 (N0-1)</p> <p>High risk of progression: Surgical T4 (any N), Surgical N2 (any T), Surgical oligometastasis</p> <p>Low risk of COVID-19: <70 year age, <2 associated disease</p> <p>High risk of COVID-19: >70 year age, >2 associated disease, immunosuppression</p> <p>Integrated risk classification</p> <p>Stage I: Low risk of progression and low risk of COVID-19 infection</p> <p>Stage IIa: High risk of progression and low risk of COVID-19 infection</p> <p>Stage IIb: Low risk of progression and high risk of COVID-19 infection</p> <p>Stage III: High risk of progression and high risk of COVID-19 infection</p> <p>Therapeutic options on the basis of the integrated classification</p> <p>Stage I: Anatomical lung resection, the early stages allow definitive oncologic treatment without the need for further hospital admission or adjuvant treatments (low risk of infection).</p> <p>Stage IIa: Anatomical lung resection (low risk of infection).</p> <p>Stage IIb: Discuss with the patient the possibility of a follow-up (up to 3 mo) before a definitive therapeutic decision after the epidemiologic peak has been overcome. Personalized treatments are evaluated.</p> <p>Stage III: Consider exclusive nonsurgical treatments.</p>
Guckenberger et al ¹⁶	<p>Early pandemic scenario 1—risk mitigation:</p> <ul style="list-style-type: none"> • Altered risk-benefit ratio of radiotherapy for patients with lung cancer in view of higher susceptibility for severe COVID-19 infection, and minimization of patient traveling and exposure of radiotherapy staff • Continue with standard recommended radiotherapy practice • Consider postponement or interruption of radiotherapy treatment of COVID-19 positive patients <p>Later pandemic scenario 2—reduced radiotherapy resources</p> <ul style="list-style-type: none"> • Triage patients requiring radiotherapy based on potential for cure, relative benefit of radiation, life expectancy, and performance status.
Mazzone et al ¹⁷	<p>Management of lung nodules and lung cancer screening during the COVID-19 pandemic</p> <ul style="list-style-type: none"> • Delay baseline or annual lung cancer screening <ol style="list-style-type: none"> 1. Delay surveillance CT/re-evaluate after 3-6 mo in cases of (a) solid nodule < 8 mm/lung RAD category 3/pure GGO/part solid with solid component 6-8 mm, (b) >8 mm solid nodule with lung RAD category 4 probability of malignancy (PM) < 10%, and (c) >8 mm solid nodule/lung RAD category 4/PM 10-25 2. Evaluate with FDG PET scan/non-surgical biopsy to ensure there is a need to proceed to treatment (surgery/SBRT) if >8 mm solid nodule/lung RAD category 4/PM 25-85% 3. Avoid further diagnostic testing and proceed to empiric treatment decision (surgery/SBRT) if >8 mm/lung RAD category 4/PM > 85%

(Continues)

TABLE 3 (Continued)

Expert groups	Recommendation
Rathod et al ¹⁸	<p>4. Delay management of stage I NSCLS after taking into consideration the assessment of size/growth rate FDG PET avidity/patient values/health and fitness status</p> <p>Recommend 4R—(1) ViRtual care, 2. Ration radiation, 3. defeR radiation, and 4. hypofRactionate radiation High priority for treatment</p> <ul style="list-style-type: none"> • Stage I-II NSCLC—SBRT; Stage II-III NSCLC—radical RTCT; limited stage (stage I-III) SCLC—radical RTCT <p>Intermediate priority for treatment</p> <ul style="list-style-type: none"> • Limited stage (stage I-III) SCLC—prophylactic cranial RT; Extensive stage (III-IV) SCLC—consolidation thoracic RT; stage IV NSCLC—palliative RT; extensive stage (III-IV) SCLC—palliative RT <p>Low priority for treatment</p> <ul style="list-style-type: none"> • Extensive stage (III-IV) SCLC—prophylactic cranial RT
Consensus Statement from Thoracic Surgery Outcomes Research Network ¹⁹	<p>Phase I</p> <ul style="list-style-type: none"> • Few COVID-19 patients in hospital with intact hospital resources intact, and COVID-19 trajectory not in rapid escalation phase • Surgery restricted to patients whose survivorship likely to be compromised by surgical delay of 3 mo <p>Phase II</p> <ul style="list-style-type: none"> • Many COVID-19 patients, with limited resources, and COVID trajectory within hospital in rapidly escalating phase • Surgery restricted to patients likely to have survivorship compromised if surgery not performed within next few days <p>Phase III</p> <ul style="list-style-type: none"> • Hospital resources are predominately routed to COVID-19 patients and resources critically limited/exhausted • Surgery restricted to patients likely to have survivorship compromised if surgery not performed within next few hours
Wu et al ²⁰	<p>Recommendations for lung cancer radiotherapy under pandemic conditions</p> <ul style="list-style-type: none"> • Early stage NSCLC—SBRT • Locally advanced NSCLC—concurrent chemoradiation, induction chemotherapy followed by radiotherapy for poor risk patients • Postoperative radiation for NSCLC—low priority • Limited-stage SCLC—surgery or SBRT; discuss pros and cons of prophylactic cranial RT vs. MRI surveillance • Extensive-stage SCLC (thoracic RT): Limited does vs. observation; discuss pros and cons of prophylactic cranial RT vs. MRI surveillance • Palliative lung RT: deferred when possible
Zhao et al ²¹	<p>Individualized medical treatment and common adverse event management for lung cancer patients during the outbreak of COVID-19 epidemic</p> <ul style="list-style-type: none"> • Prevention of infection: lung cancer patients should stay at home and minimize going outside; exercise; have adequate sleep and nutritious diet; monitor temperature and respiratory symptoms. • Postoperative lung cancer patients awaiting treatment: delay adjuvant therapy after surgery by 4 mo; consider TKI as adjuvant therapy for N2 disease • Advanced lung cancer: antitumor treatment at the earliest is recommended, if possible. Consider convenient alternatives, such as oral-targeted drugs or chemotherapeutic agents at the nearest experienced hospital • Lung cancer patients undergoing chemotherapy: Low tumor burden and stable disease/those undergoing postoperative adjuvant chemotherapy/maintenance treatment: Chemotherapy in hospital can be appropriately postponed or switched to oral chemotherapy with targeted drug administration at home • Lung cancer patients undergoing targeted therapy: Lung cancer patients with sensitive gene mutations can be treated with oral targeted drugs during the outbreak, without combination therapy. Attention should be paid to the adverse events of some targeted drugs. Patients whose symptoms are obviously relieved after targeted therapy and those with stable disease can be appropriately deferred to the hospital for review during the epidemic • Lung cancer patients undergoing immunotherapy: During the epidemic, it is not urgent to receive immunotherapy on a set date. Considering the adverse events of potential pulmonary

TABLE 3 (Continued)

Expert groups	Recommendation
	<p>toxicity or injury caused by immunotherapeutic drugs, immunotherapy can be suspended or postponed in patients with stable disease</p> <ul style="list-style-type: none"> • Regular examination of lung cancer patients: For early-stage postoperative lung cancer: can be delayed. For advanced lung cancer patients receiving targeted therapy: can be appropriately postponed or delayed on the basis of the cancer conditions

Lung and thoracic malignancies

Overall, 32 articles addressing the effect of COVID-19 on lung and thoracic malignancies were retrieved. Seven articles were in the Chinese language. Table 3 displays various guidelines or recommendations by various societies and expert groups for the management of lung cancer and thoracic malignancies during COVID-19 pandemic.^{14,16-22} There was a high discordance in the recommendations—three of them^{14,22,23} recommend standard treatment to continue, with a suggestion to alter the management in case of rising trend of SARS-Cov-2 infection; two of them^{18,20} do not recommend surgery for early lung cancers and instead recommended stereotactic body radiotherapy (SBRT); another two guidelines^{16,19} suggest to triage the patients based on the tumor stage, clinical condition, risk of SARS-CoV-2 infection, and availability of resources. One guideline¹⁷ addresses the management of lung nodules and suggests a delay in diagnostic testing. Table S2 displays four case series and six case reports of lung cancer patients with COVID-19 infection, respectively.²⁴⁻³³

Breast cancer

There were 13 articles that addressed the impact of COVID-19 pandemic on the management of breast cancer. Full texts of five articles were not present in the English language. Table 4 displays various guidelines/recommendations for the management of breast cancer during COVID-19 pandemic.³⁴⁻³⁷ All the guidelines have a high concordance in recommending triage of the patients with breast cancer based on the patient and the tumor factors in the present crisis. The indications of the radiotherapy were shelved in patients with low-risk features while delaying or hypo-fractionating the dose was recommended in patients with high-risk features for disease recurrence. Guidelines for surgery are not objective and have discordance in recommendations—Curigliano et al³⁶ recommend the most effective but minimal surgical procedures for patients with early breast cancer; the COVID-19 pandemic breast cancer consortium³⁷ suggest that a delay of 6 to 12 weeks if surgery is unlikely to affect the outcome.

Gynecological cancers

A total of nine articles addressing the effect of COVID-19 on gynecological cancers were retrieved. Two of them were not available in the English language. Table 5 displays the various guidelines or recommendations by various societies or expert groups to manage the gynecological cancers during the COVID-19 pandemic.³⁸⁻⁴² In advanced gynecological cancers, all guidelines uniformly recommend

neoadjuvant chemotherapy or definitive chemoradiation therapy; however, there is a discordance in recommended timing for surgery for early cancers. FRANCOGYN group³⁸ recommend deferring the surgery by 1 to 2 months while Bhatla et al³⁹ suggest surgery if the risk for COVID-19 is low and the health-resources permit. There is also ambiguity about the role of using minimally invasive surgery—though the majority of the guidelines suggest not using laparoscopic procedures, Society of European Robotic Gynaecological Surgery (SERGS) recommend that Robot-assisted surgery may prove to be a safe surgical option if all the necessary precautions (protective kits and prevention of the free escape of CO₂ and aerosol) are followed. There was also a case series of three patients reported from a medical center in Wuhan, China. These three patients had undergone surgery for gynaecological tumors (malignant—2, benign—1) and developed COVID-19-related pneumonia in the postoperative period. Two of them recovered well and were discharged; however, one was still admitted in the hospital at the time of submission of the report.⁴³

Urological cancers

A total of 12 articles concerning the impact of COVID-19 on the management of urological cancers were retrieved. All the articles addressed either bladder or prostatic cancer. The maximum number of the articles (n = 8) were letters/comments/personal perspectives while there were two editorials, one recommendation, and one survey. A retrospective review of the 128 062 men with intermediate and high-risk prostate cancer (PC) in the National Cancer Database (NCDB) undergoing radical prostatectomy (RP) from 2010-2016 highlighted that delayed RP (from 3 to 12 months) was not associated with the worse oncological outcomes compared with patients undergoing immediate (within 3 months) RP.⁴⁴ This finding may provide solace to the patients with prostatic cancer, who are waiting for surgery during this time of COVID-19 pandemic.

Colorectal cancer

The impact of the COVID-19 epidemic over the management of colorectal cancer was addressed in 12 articles. Four of them were personal viewpoints/commentary/perspectives while there was one editorial and a case report. Six of them were guidelines/recommendations by various societies/expert groups. Full text of the five articles was not available in the English language. Di Saverio et al⁴⁵ divided the colorectal cases into three categories: (a) High priority cases to be operated within 2 weeks—cancer-associated emergencies, which are not amenable for nonsurgical treatment, (b) Intermediate priority cases to be operated within

TABLE 4 Guidelines/recommendations for the treatment of breast cancer during Covid-19 pandemic

Author/group	Recommendations
Braunstein et al ³⁴	<p>Different levels of priorities for radiotherapy for patients with breast cancer</p> <p>(a) High—Inflammatory breast cancer, residual node positivity after NAC, 4 or more positive nodes (N2), recurrent disease, node-positive TNBC, extensive LVI.</p> <p>(b) Intermediate—ER+ with 1-3 positive nodes (N1a), Path N0 after NAC, LVI (NOS), Node-negative TNBC</p> <p>(c) Low—early-stage ER+ breast cancer (older patients), DCIS, Otherwise not meeting criteria for high or intermediate priority</p>
Coles et al ³⁵	<p>International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic</p> <ol style="list-style-type: none"> Omit RT for patients 65 y and over (or younger with relevant comorbidities), with invasive breast cancer that are up to 30 mm with clear margins, grade 1-2, estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative and node negative, who are planned for treatment with endocrine therapy Deliver RT in 5 fractions only for patients requiring RT with node-negative tumors that do not require a boost. Options include 28-30Gy in once weekly fractions over 5 wk or 26 Gy in 5 daily fractions over 1 wk as per the FAST and FAST Forward trials, respectively. Boost RT should be omitted to reduce fractions and/or complexity in the vast majority of patients unless they 40 years old and under, or over 40 years with significant risk factors for local relapse. Nodal RT can be omitted in postmenopausal women requiring whole breast RT following sentinel lymph node biopsy and primary surgery for T1, ER positive, HER2 negative G1-2 tumors with 1-2 macrometastases. Moderate hypofractionation should be used for all breast/chest wall and nodal RT, for example 40 Gy in 15 fractions over 3 wk
Curigliano et al ³⁶	<p>Recommendations for triage, prioritization and treatment of breast cancer patients during the COVID-19 pandemic</p> <p>Screening and diagnosis: suspend population mammographic screening, avoid delayed diagnosis [BIRADS 5 (high priority) or BIRADS 4 (medium priority)]</p> <p>Early breast cancer:</p> <ol style="list-style-type: none"> Surgery: Prefer the most effective minimal surgical procedure with the fastest recovery time Radiation: Postpone RT up to 3 mo for high-risk and up to 6 mo for low-risk patients; Moderate hypofractionation; Omit boost RT in patients with low risk for local relapse; Consider accelerated partial breast RT low-risk patients; consider omission of RT in elderly patients at low risk of recurrence Systemic therapy: Avoid drugs with risk of immunosuppression; limit use of steroids; prefer 3 weekly regimen; recommend anti-HER2 agents for HER2⁺; follow usual international guidelines for adjuvant endocrine therapy; prefer oral formulations for adjuvant bisphosphonates. <p>Advanced breast cancer:</p> <ol style="list-style-type: none"> Systemic therapy: consider dose reductions and dose interruptions; consider treatment holidays in prolonged treatments and stable disease; prefer endocrine-based therapy for ER⁺/HER2 negative; individualize the use of CDK 4/6 and mTOR inhibitors; prefer oral and liposomal formulations when using chemotherapy; consider use of prophylactic hematopoietic growth factors. Radiation: urgent for spinal cord compression, brain and leptomeningeal metastases, and palliative treatments (eg of bone metastases) not responding to pharmaceutical interventions
Dietz et al, ³⁷ The COVID-19 pandemic breast cancer consortium	<p>Recommendations for prioritization, treatment, and triage of patients with breast cancer during the COVID-19 pandemic.</p> <p>Surgical oncology</p> <ol style="list-style-type: none"> Priority A (life threatening)—breast abscess in a septic patient, Expanding hematoma in a hemodynamically unstable patient Priority B (not immediately life-threatening conditions but for whom treatment or services should not be indefinitely delayed until the end of the pandemic—most patients with breast cancer; a delay of 6-12 wk is unlikely to impact the overall survival. Priority C (can be indefinitely deferred until the pandemic is over without adversely impacting outcomes)—pre-invasive cancer; breast reconstruction. <p>Medical oncology</p> <ol style="list-style-type: none"> Priority A (life threatening)—oncologic emergencies requiring immediate treatment (eg febrile neutropenia, intractable pain) Priority B—require systemic therapy but modified therapeutic approaches to minimize patient interactions with healthcare centers, maintain patient safety, and conserve resources while providing effective care Priority C—delay interventions for many months without adverse impact on survival or quality of life. <p>Radiation oncology</p>

TABLE 4 (Continued)

Author/group	Recommendations
	<ol style="list-style-type: none"> 1. Priority A—includes patients presenting with symptomatic disease in whom short palliative RT regimens should be utilized 2. Priority B—majority of patients; stratify them based on clinicopathological parameters 3. Priority C—delaying RT does not affect survival outcomes (eg most DCIS, patients ≥ 65–70 y with early stage, node negative, ER + invasive disease)

2 months—cancer curable with surgery without any adjuvant treatment, (c) Low priority cases to be deferred for more than 2 months— (i) Cancer amenable to radiation, pharmacological, and endoscopic treatment, and (ii) early cancer with good biology. The authors recommend that patients with a surgically curable disease but COVID-19 positive should be treated conservatively as much as possible without subjecting them to unnecessary risk.

3.5.2 | Hematological malignancies

A total of six articles were retrieved on this topic of which full text of one article was in the Chinese language. Table S3 provides a brief overview of recommendations to help physicians to choose evidence-based information in light of the current scarcity of medical resources. The available literature also supports administering prophylactic antibacterial, antiviral medications, optimizing antiemetics and analgesic doses to reduce the hospital visits.⁴⁶

3.5.3 | Radiation therapy related

A total of eight articles concerning the various challenges observed while delivering radiation therapy was retrieved. Full texts of the two articles were not available in the English language. The remaining six articles were either recommendations, or suggestions, or opinions of expert groups to optimally deliver the radiation therapy while safeguarding the healthcare workers and limiting the effects of COVID-19 on the patients receiving radiation therapy.

3.5.4 | Cancer chemotherapy/immunotherapy related

A total of five articles addressing the cancer chemotherapy/immunotherapy were retrieved. Two of them were short communications/correspondences while one was an editorial. Out of the remaining two, one reviewed the literature to determine the association of cytotoxic chemotherapy and host immunity for COVID-19 and concluded that they do not have any beneficial action in mitigating the COVID-19-related effects.⁴⁷ Another was a survey conducted by the Collegio Italianodei Primari Oncologi Medici (CIPOMO) to assess the effect of COVID-19 on the clinical practice of the oncologists and the implementation of various measures to

contain COVID-19 infection. They concluded that the oncologists need to continue anticancer treatment while strictly adhering to anti-COVID-19 measures as the benefit of anticancer therapy outweighs the risk of COVID-19 infection.⁴⁸

4 | MISCELLANEOUS

A total of 47 articles could not be classified separately into defined groups and were classified as miscellaneous. Majority of them (n = 15) were primarily recommendation or guidelines or reviews by various societies/expert groups while others were editorials (n = 9) or short communication/Comments/Personal opinion/Letter to editor/Perspective/News articles (n = 16) and addressed the impact of COVID-19 pandemic on cancer research, clinical characteristics, and coping strategies for COVID-19-infected cancer patients, challenges, and countermeasures in cancer care delivery. Table S4 displays the relevant findings of five of the seven research articles/surveys. Full texts of the remaining two articles were not available in the English language.⁴⁹⁻⁵³ Majority of the publications highlighted a higher incidence of adverse events in case of administration of anticancer treatment—surgical or cytotoxic chemotherapy. Trans-Tasman Radiation Oncology Group (TROG) noted that live virtual meeting is a safe and viable platform for the dissemination of knowledge among the cancer experts during global health crisis.⁴⁹

5 | DISCUSSION

There is a plethora of literature addressing COVID-19 and cancer published in the last 4 months. While guidelines are helpful in the management of disease with limited evidence, it is important to recognize that these are not definitive experimental trials/designs. COVID-19 pandemic has also brought the notion of “primum non nocere” (first, do no harm) into the scrutiny as actions taken in the anticipation of success during the difficult time of pandemic may prove to be futile in retrospection.

The heterogeneity of articles providing various recommendations/suggestion to tackle the COVID-19, with differing level of evidence, can make it difficult for physicians, patients, and healthcare systems to adopt uniform strategies. As speculations continue over the possibility of further extension of the COVID-19 outbreak, the oncology community must be prepared for the fact that delivering a high level of care to cancer patients will become a daunting task. Hence, there is an urgent need to strike a balance between delivering

TABLE 5 Guidelines/recommendations for the treatment of major gynaecological neoplasms during Covid-19 pandemic

Expert groups	Recommendation
Akladios et al, FRANCOGYN group ³⁸	<p>Ovarian cancer: Early stage—defer surgery by 1-2 mo; Advanced stage—neoadjuvant chemotherapy; HIPEC not recommended Endometrial cancer: low risk, early stage—defer by 1-2 mo; high risk early stage—lymphadenectomy as per MSKCC criteria; advanced stage—medical therapy Cervical cancer: Radiotherapy and concomitant chemoradiotherapy preferred over surgery Vulval cancer: No change Vaginal cancer: majority are advanced—chemotherapy/radiotherapy Trophoblastic tumors: Low risk—home based methotrexate; high risk—multiagent chemotherapy Post-oncological treatment follow-up: postpone by 2 mo</p>
Bhatla et al ³⁹	<ol style="list-style-type: none"> 1. Low acuity surgery: postpone surgery for few weeks or months (example pre-invasive lesions of cervix or endometrium) 2. Intermediate acuity surgery: low-risk cancer—postpone surgery if possible or consider early discharge. 3. High acuity surgery: Do not postpone if COVID census is low and resources permit—most cancers, highly symptomatic patients (type II endometrial cancers, ovarian cancer, interval debulking surgery after 3-4 cycles of chemotherapy, uterine sarcoma, those in need of emergency procedures, excision of malignant recurrences, GTN) <p>*A multidisciplinary team discussion and planning of therapy preferred before surgery* *Avoid laparoscopic procedures</p>
Italian Society for Colposcopy and Cervico-Vaginal Pathology (SICPCV) group ⁴⁰	<p>Patients to be evaluated within 2-4 wk—Cytology result of “squamous cell carcinoma,” “atypical glandular cells, favor neoplastic,” “endocervical adenocarcinoma in situ,” or “adenocarcinoma”; histopathological diagnosis of suspected invasion from cervical/vaginal biopsy, or invasive disease after a cervical excision procedure, vaginal excision, or vulvar biopsy/excision; sudden onset of strongly suggestive symptoms for malignancy Patients to be evaluated within 3 mo—Patients with “high-grade squamous intraepithelial lesion (HSIL),” “atypical squamous cells that cannot exclude HSIL (ASC-H),” or “atypical glandular cells not otherwise specified (AGS-NOS)” at cervical cytology; Patients with a histopathological diagnosis of high-grade intraepithelial lesion without suspicion of invasion from a cervical biopsy (HSIL, CIN2-3), vaginal biopsy (HSIL, VAIN2-3), or a vulvar biopsy/excision (vulvar HSIL or differentiated VIN). Patients to be evaluated within 6-12 mo—Contact with patients with “positive high-risk HPV test with normal cervical cytology,” “low-grade squamous intraepithelial lesion (LSIL),” or “atypical squamous cells of undetermined significance (ASC-US)” at cervical cytology 7 or with a histopathological diagnosis of low-grade intraepithelial lesion from a cervical, vaginal, or vulvar biopsy/excision</p>
Society of European Robotic Gynaecological Surgery (SERGS) statement ⁴¹	<p>Robot-assisted surgery may prove to be a safe surgical option if all the necessary precautions (protective kits and prevention of free escape of CO₂ and aerosol) are followed.</p>
Remirez et al (Editorial Team of the International Journal of Gynecological Cancer) ⁴²	<p>Ovarian cancer:</p> <ol style="list-style-type: none"> (a) Early disease, consideration of multiple factors, to assess risk of malignancy in adnexal mass. (b) Advanced stage disease—neoadjuvant chemotherapy until crisis is resolved and consider surgery at a later time. (c) Patients on neoadjuvant chemotherapy—consider extending the treatment plan to six cycles <p>Endometrial cancer:</p> <ol style="list-style-type: none"> (a) Low-risk patients: Consider for conservative management with nonsurgical options, including systemic hormonal therapy or intrauterine devices. (b) High-risk patients: Consider simple hysterectomy and bilateral salpingo-oophorectomy alone ± sentinel lymph nodes, if available and feasible (c) Advanced disease: systemic therapy. <p>Cervical cancer:</p> <ol style="list-style-type: none"> (a) Pre-invasive disease—low risk: postponement of diagnostic evaluations for 6-12 mo; high risk—diagnostic evaluation scheduled within 3 mo (b) Early-stage Invasive cancer—Standard care needed if oncological surgeries are allowed at the center, else consider postponement of high-risk procedures or consider for conization or simple trachelectomy ± sentinel lymph nodes for low-risk disease or neoadjuvant chemotherapy

TABLE 6 Postulated reasons for discordance among the guidelines

- A rapid response to the pandemic—various institutional policies were formulated without multicentric discussion.
- Paucity of literature—The outcomes of oncological treatments in form of delaying surgery, chemotherapy/immunotherapy or radiation therapy in the patients with active or latent SARS-CoV-2 infection is currently an unfathomed territory.
- Differences in the national healthcare systems (single-payer system, government-run care, hybrid system, etc), which have a considerable impact while formulating any guidelines.
- Demographic profile of the nation as well as the percentage of population affected by COVID-19 and the relative proportion of healthcare resources available.
- Lack of mental preparedness and unanticipated clinical outcomes of the pandemic.
- All the guidelines/consensus statements are framed in a relatively short period of time without multilevel comprehensive discussions supported by the sufficient evidence.

All the guidelines/consensus statements clearly mention that they can be subjected to constant evolution and dynamism in light of emerging new evidence.

safe and effective care to cancer patients, including triaging of surgical patients and simultaneously conserving national healthcare resources. There is an urgent need for consolidating multiple guidelines to derive a conclusive evidence-based approach available to the practising oncologist.

Most of the recommendations indicate that alternative safe cancer care therapies should be discussed in the management of the patients with cancer in multidisciplinary meetings to safeguard them from the COVID-19-related adverse effects. However, the current crisis should not be taken as an excuse to lower the standards of healthcare interventions. The status of the pandemic in a particular region, availability of resources, and various patient and tumor-related factors must be simultaneously taken into consideration during decision-making. The use of the virtual technologies to conduct multidisciplinary tumor boards and teleconsultations have provided a major thrust to delivering cancer care in the time of the pandemic. However, providing optimum surgery to the patients when nonsurgical treatment options are not available and any delay can adversely affect the patient survival outcomes can be challenging. There is concordance in the guidelines suggesting a nonsurgical approach for patients with advanced cancers; however, there is discordance about the role of surgery in early-stage tumors. Delay in surgery for potentially curable early tumors is a major conflict among the guidelines. Table 6 highlights the likely reasons for these discordances among these guidelines.

There is an urgent need for formulating evidence-based practice guidelines for various domains of oncology practice so as to ensure the delivery of high-quality treatment. Global crowdsourcing⁵⁴ has the potential to help establish such evidence-based guidelines.

5.1 | Limitations of the review

Our search strategy, while systematic, did not include all published guidelines due to the rapid pace of publication. There is significant heterogeneity and limited data in the articles included.

6 | CONCLUSION

COVID-19 pandemic has posed dilemmas for the oncology community across the globe. Guidelines based on limited evidence show discordance and need to be interpreted with caution. “Crowdsourcing” could help collate the data related to COVID-19 and generate high-quality evidence-based guidelines.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conception and design: PKG, PK, KKT, VA, NA, BR, SY; collection and assembly of data: PKG, PK, DC, MPS, ART; Data analysis and interpretation: PKG, PK, KKT, NA, BR, SY, DC, MPS, ART; manuscript writing: all authors; final approval of manuscript: all authors; accountable for all aspects of the work: all authors.

DATA AVAILABILITY STATEMENT

The data that support the finding of the study is available in the public domain and has been cited in the reference section.

ORCID

Pankaj Kumar Garg  <http://orcid.org/0000-0001-9760-5484>

Pallvi Kaul  <http://orcid.org/0000-0003-4003-6430>

Deepti Choudhary  <https://orcid.org/0000-0001-9408-9111>

Kiran Kalyan Turaga  <http://orcid.org/0000-0001-8541-586X>

Mahendra Pal Singh  <https://orcid.org/0000-0002-3734-2093>

Ajeet Ramamani Tiwari  <https://orcid.org/0000-0002-4610-4142>

Vipin Arora  <https://orcid.org/0000-0003-1770-4234>

Beat Rau  <https://orcid.org/0000-0001-5820-6907>

Sai Yendamuri  <https://orcid.org/0000-0001-6654-3487>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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