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Radiation oncology in times of COVID-2019: A review article for those in the eye of the storm – An Indian perspective

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ABSTRACT

The global COVID-2019 pandemic has presented to the field of radiation oncology a management dilemma in providing evidence-based treatments to all cancer patients. There is a need for appropriate measures to be taken to reduce infectious spread between the medical healthcare providers and the patient population. Such times warrant resource prioritization and to continue treatment with best available evidence, thereby reducing the risk of COVID-2019 transmission in times where the workforce is reduced. There has been literature presented in different aspects related to providing safety measures, running of a radiation department and for the management of various cancer subsites. In this article, we present a comprehensive review for sustaining a radiation oncology department in times of the COVID-2019 pandemic.

Introduction

The world, as we write this review, is facing a pandemic of catastrophic proportions in the form of Novel Coronavirus (COVID-2019) [1], first identified in Wuhan, in Hubei principality in China in December 2019 [2]. The pandemic hit the Indian healthcare scenario in the most unanticipated manner, with numbers in China and the European Union on the rise. While at the time of this writing the number of cases in India have not been overwhelming, healthcare workers and the healthcare system have tried to take swift actions in the hopes of preventing the devastation that has occurred in America and Europe. Public health workers believe that the pandemic will escalate and it will continue to last for a long time [3] Oncological institutes specifically, have been especially impacted as they address the management of their patients and devise plans to provide treatment options for already immunocompromised patients as they have shown to have a five-fold relative risk for severe manifestations compared to the general population [4]. The literature from various oncological institutes and societies has paved the way for a better understanding of the management of the disease. Various institutions have described their experiences in individual publications. Here we attempt to present a comprehensive review of the literature published related to the handling of radiation oncology setups and the management of various cancer subsites during the COVID-2019 pandemic.

Methodology

We performed a PubMed search with the following MesH terms: Coronavirus, COVID-2019 AND Oncology, Coronavirus AND radiation therapy, Coronavirus AND radiation oncology along with the articles published in the various oncology societies through google search and the individual websites. A total of 19 articles were found to be suitable for the review. The focus was on the best available practice in terms of radiation therapy in institutes that addressed the medical professional working protocols, guidance for individual disease sites and safety measures while handling this patient population.

COVID-19 specific guidelines

Prevention or mitigation of transmission forms the basic priority while managing patients, especially those with a diagnosis

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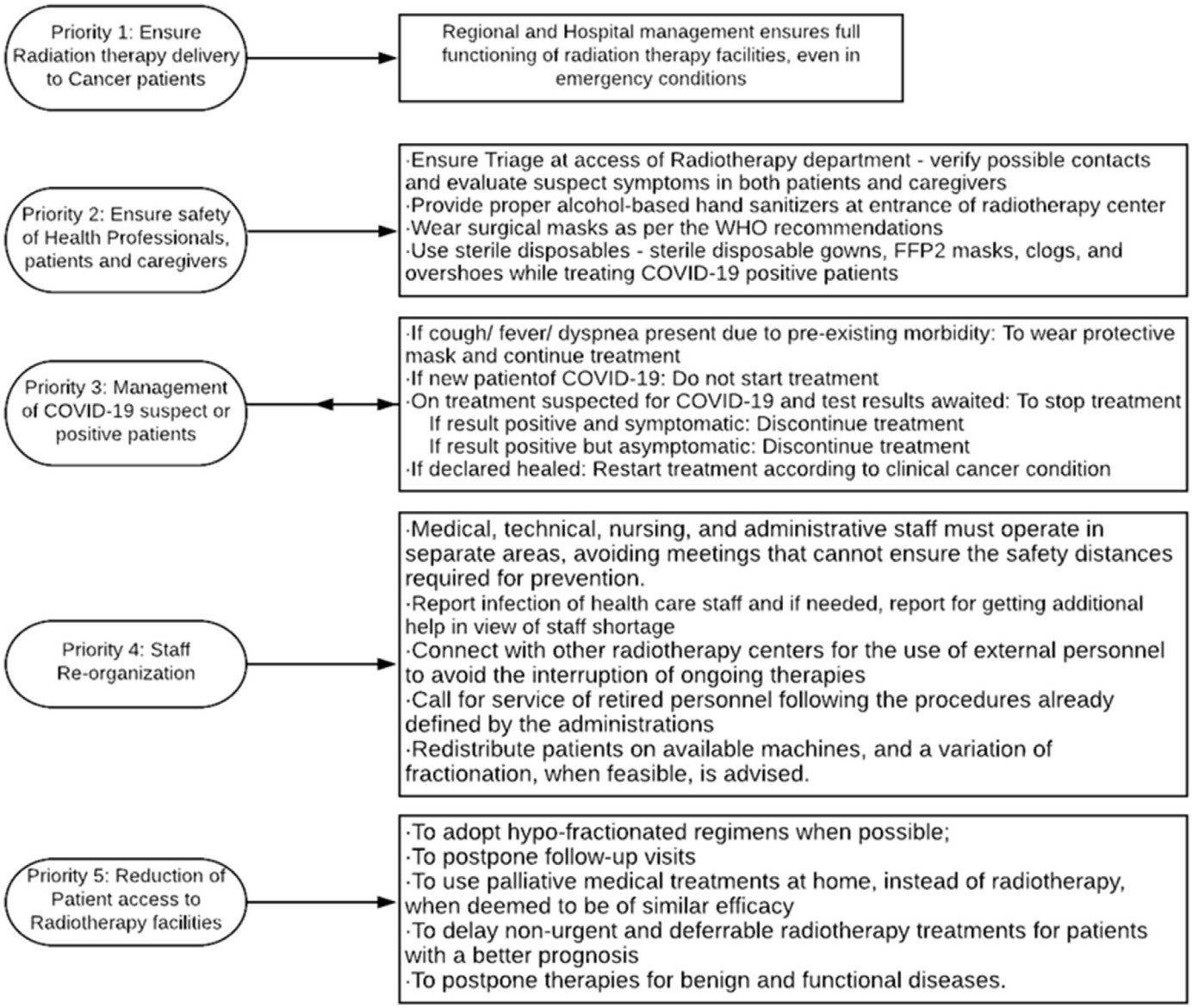

Fig. 1. Priority levels in COVID management in Radiatherepy centers.

of cancer and providing optimum supportive measures. The guidelines mentioned in the literature can be divided into various priority levels or tiers of management. The priority levels as defined by Fillipi et al are illustrated in Fig. 1 [5].

Other specific measures

Dinh et al [6], present additional guidelines in terms of patient care, mitigation of disease transmission and training of residents in radiation oncology as well as the healthcare staff. These recommendations are enumerated below:

1. Employees who can perform duties remotely (eg, research coordinators, research residents, administrative staff, and some medical physics staff) should be instructed to work from home.
2. Meetings should be limited to five persons or less, with at least 6 feet of distance between any two individuals.
3. Tumor boards should be transitioned to virtual conferencing, except for small meetings with five persons or less, with exceptions made only for a tumor board in which in-person coordination is felt indispensable to patient care.
4. New patient consultations for treatment of indolent or benign conditions should be deferred at the discretion of the radiation oncologist.
5. Routine follow-ups should be offered to patients via telephone or postponed.
6. To conserve PPE, institute policies limiting the number of providers required to come into direct contact with patients with suspected or confirmed COVID-19.
7. Immobilization devices such as VacLoc bags should be individually disinfected and wrapped in a plastic bag that is sealed and changed after each daily use.
8. Treatment tables and positioning aides should be extensively disinfected between patients.
9. Active breathing controller (ABC, Elekta Inc.) should not be used in suspected or confirmed cases and abdominal compression should be used instead.

Also, in correspondence from Tata Memorial Hospital, Mumbai by Mummadi, et al, elaborated on the nuances and finer details associated with running a radiation oncology department in times of a pandemic. The salient features about the patient care in times

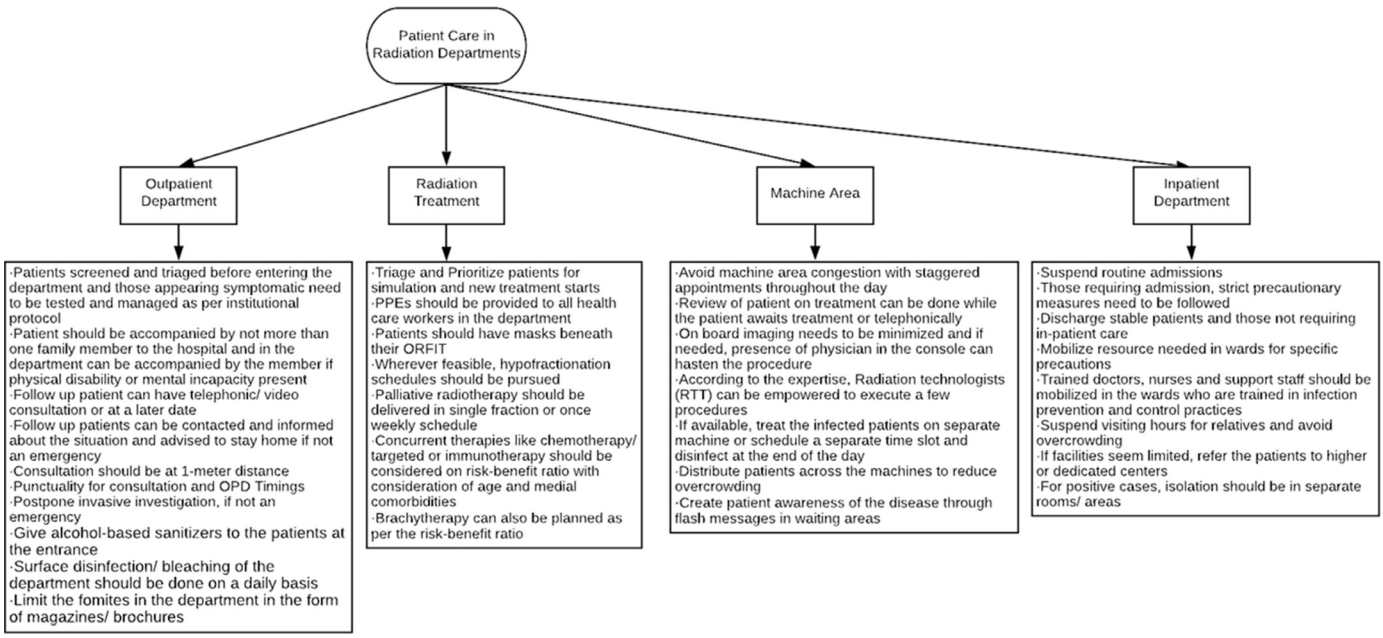

Fig. 2. Patient Care in Radiation Oncology department in COVID times.

of COVID-2019 while running the radiation oncology department, have been highlighted in Fig. 2.

Treatment priority according to disease site

Oncological decisions have been evidence-based and level I evidence has been chased while delivering optimum treatment. However, pandemics like the COVID-2019 provides a dilemma and an ethical challenge because of limited resources and elevated risks of infections in treating with evidence-based practice. Such times demand appropriate treatment decisions that require a careful balance of patient benefits and associated risks. This warrants the need to look into phase II trials, prospective evidence and also some retrospective series. The harm associated with COVID infection in cancer patients has been presented by a simple model by Simcock, et al [7] If a patient has a 5% risk of infection and a 10% risk of death from infection there may be a 0.5% mortality through exposure and attendance for radiotherapy. If the patient is young and healthy with a 5% risk of infection and a 1% risk of death, then there is a 0.05% mortality from COVID-19. The use of chemotherapy in combination with radiotherapy is likely to significantly increase the risk of morbidity and mortality from synchronous COVID-19 infection. The various disease sites have been discussed with the look into the available literature.

Central Nervous System (CNS)

Available guidelines in the wake of the pandemic coming from the various neuro-oncology societies have been limited. The available literature in view of disease mitigation and appropriate treatment approaches are presented in Table 1 and the priority given to the management of CNS tumor is shown in Figs. 3 and 4.

Head and neck malignancies

Radiation therapy with concurrent chemotherapy forms the mainstay in the majority of head and neck malignancies with a tendency towards improved survival and providing the option of organ preservation. In India, head and neck malignancies form the major bulk of disease and hence management options need to be meticulous. As with other subsites, a multi-disciplinary board needs to weigh the risk-benefit ratio and chose the best available modality suitable for the patient without severely compromising their oncological outcome. The available recommendations for head and neck malignancies are enumerated in Table 1.

Breast cancer

Radiation therapy for patients with breast cancer contributes to a significant proportion of the workload in any radiation oncology department. Knowledge about priorities and exercising these to decrease unnecessary patient visits will significantly impact radiation facility resources. In the present resource strained COVID-19 pandemic situation, it is important to prioritize patients and consider low-risk situations where delaying/de-escalating or omitting treatment may not be so detrimental yet save resources for other more pressing indications. Table 1. illustrates the best available evidence for the management of various stages of breast cancer and indicates the techniques that can be used for boost delivery.

Fractionation. Hypo-fractionated radiation therapy is widely accepted for whole breast radiation therapy. 42.5 Gy in 16 fractions or 40 Gy in 15 fractions are commonly utilized regimens. Especially in the present pandemic situation, 50 Gy in 25 fractions should be deferred. Newer, still shortened and accelerated regimens are finding their place. There is 3 years toxicity data showing equivalence in toxicity for 28.5 Gy in 5 fractions (once a week) as compared to the 15 fractions regimens and acute toxicity results for 26 Gy in 5 daily fractions.

Accelerated partial breast irradiation. Accelerated partial breast irradiation (APBI) involves partial breast irradiation (tumor cavity with adequate margin), delivered in an accelerated regimen over 1-2 weeks. It has been an acceptable treatment option for more than a decade now. APBI can be offered to women with infiltrating ductal carcinoma over 60 years, tumor size up to 2 cm, node-negative, ER+, no Lymphovascular Stromal Invasion (LVSI), and clear margins. Target volume includes the surgical cavity with

Table 1
Management of Various malignancy sites during COVID-19 – Part 1

GUIDELINES FOR CNS TUMORS

1. GBM in >60 yrs, methylated status → Temozolomide alone [8,9]
2. Asymptomatic Meningioma Grade 1-2 → Omit Radiotherapy
3. Asymptomatic arteriovenous malformation (AVM) → Omit radiotherapy
4. Grade 3 glioma:
   - 1p19q co-deleted (anaplastic oligodendroglioma) → Can consider delay in radiotherapy and chemotherapy for 4-6 months
   - Non-co-deleted (anaplastic astrocytoma) → Deliver radiation therapy and delay chemotherapy for 4-6 months; Post RT imaging at 3 months
5. Hypofractionated regimens in RT:
   - 40 Gy/15 fractions
   - 30 Gy/6 fractions
6. Consider delaying the control MRI appointments in asymptomatic, long-term survivors of less malignant brain tumors, e.g., meningiomas, schwannomas.

GUIDELINES FOR HEAD AND NECK MALIGNANCIES

Curative treatment – High priority patients

1. Hypofractionated radiotherapy can be considered
   - 65 Gy in 30 fractions can be considered
   - 55 Gy in 20 fractions over 4 weeks [10]
2. Concurrent chemotherapy use can be restricted to patients < 60 years as the benefit decreases with advancing age [11]
3. Accelerated fractionation without chemotherapy (6 fractions per week) / Simultaneous integrated boost approach [12]

Adjuvant treatment

1. Consider omitting adjuvant chemotherapy
2. Patient with R0 resection and minor risk factor – can consider omitting radiation therapy

Palliative treatment

1. Deliver only when benefits outweigh the risk
2. Consider short fractionation schedules:
   - 25 Gy in 5 fractions
   - 20 Gy in 5 fractions
   - 30 Gy in 6 fractions
   - IMRT over 2 weeks
   - Single 8 Gy fraction [13,14]
3. Do not start or delay palliative chemotherapy/ immunotherapy

Other Considerations:

1. Patients with laryngectomy / tracheostomy should be treated only if proper protective measures are available as maximum aerosol dispersion is present in such cases
2. Omit cisplatin-based induction chemotherapy [15]
3. Delay post-operative RT in patients with salivary gland tumors until 12 weeks after surgery. Time factor is not strictly linked to adverse effect in these cases [16]

GUIDELINES FOR BREAST CANCER: DIFFERENT PRESENTATIONS OF LOCALIZED CARCINOMA OF THE BREAST AND REASONABLE OPTIONS TO DE-ESCALATE TREATMENT

Presentation	Recommendation
Ductal carcinoma in situ (DCIS)	• Good risk → Omit RT. If planned, can delay up to 12 weeks [17,18] • Others → Can consider omission. If planned, it can be delayed up to 12 weeks [19]
Early breast cancer (EBC)	• Age >70 yrs, post breast-conserving surgery (BCS) - T1, N0, ER+(receiving ET), margins clear → May omit RT [20] • Age >65yrs, ER+, N0, T1/T2 (up to 3 cms), clear margins; grade 3 or LVI [21] • Young premenopausal women → Proceed with RT as scheduled. • EBC post BCS: If RT without chemotherapy is planned → can be delayed up to 20 weeks post BCS [22]
Locally advanced breast cancer (LABC)	• LABC → Proceed with RT as scheduled
Good risk DCIS:	• Low/intermediate grade, <2.5 cms, margin >3 mm. → If omission/delay in RT is planned for ER/PR+ EBC/DCIS, endocrine therapy can be initiated immediately

Boost dose recommendations:

Disease type	DCIS	Early breast cancer (EBC)
Recommendation	**May be omitted** Less than 2% benefit in Ipsilateral breast tumor recurrence rate at 10 years, less than 4% benefit at 15 years. [23,24] Caution in women less than 40 years (significant benefit)	• **May be omitted in elderly (>60 years)** → Improves local control, no impact on OS, Largest benefit in young women • **Hypofractionate** • **SIB (simultaneous integrated boost) or concomitant boost -** daily or weekly can be incorporated to decrease treatment time • **5.2 Gy single fraction boost** → May be considered after ultra-hypofractionated regimens [25]

Prioritizing radiation services in breast cancer during COVID-2019

Tier 1 (continue radiation)	Tier 2 (short delay acceptable)	Tier 3 (omit)
• Inflammatory breast cancer • Residual nodal disease after NACT • N2 disease (4 or more nodes) • Recurrent disease • Node positive TNBC • Extensive LVI	• ER+ disease with N1a nodes (1-3 nodes) • Node negative TNBC • Pathological N0 post NACT • LVI (not otherwise specified)	• Early stage ER+ breast cancer especially in elderly • DCIS

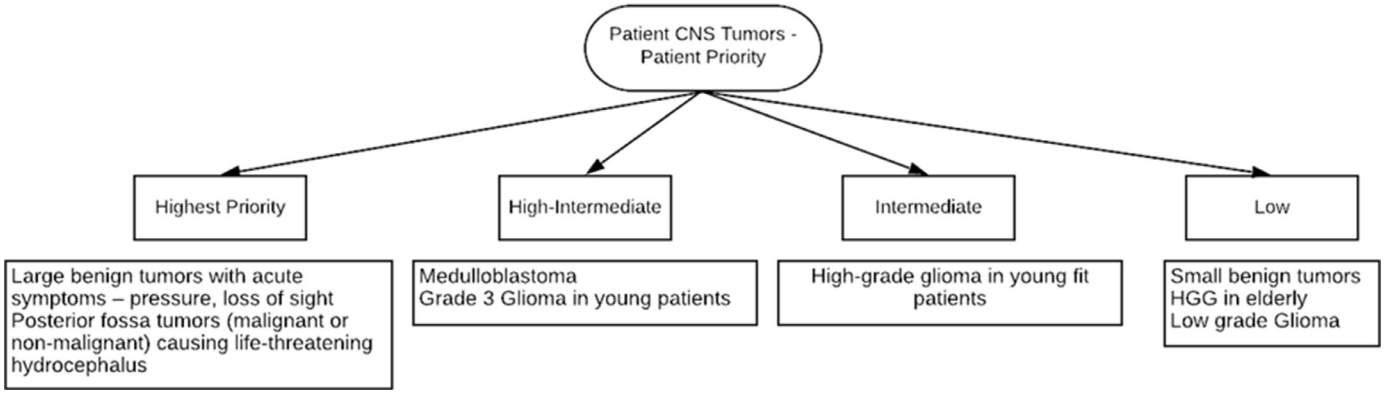

Fig. 3. Patient Priority based management in CNS Tumors.

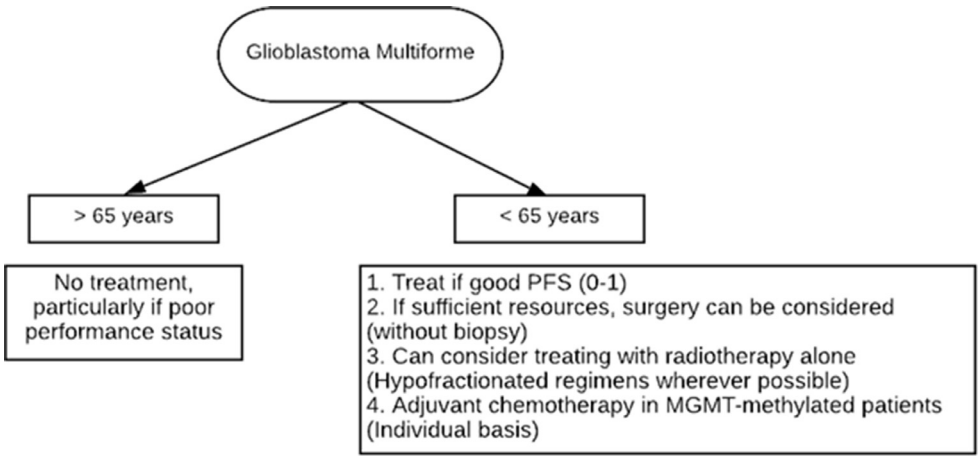

Fig. 4. Algorithm for management decisions for GBM.

a margin. APBI can be delivered through balloon brachytherapy, interstitial brachytherapy, and external beam radiation therapy. However, in the present COVID-19 pandemic, it is advisable to do using external beam radiation therapy using 3DCRT or Intensity Modulated Radiation Therapy/Volumated arc Therapy (IMRT/VMAT) as brachytherapy would require additional resources and also would lead to unnecessary exposure and hospital stay. It may also increase the risk of transmission during intubations or upper endoscopic procedures and necessitate increased PPE while they are in short supply. Regimens include 30 Gy in 5 fractions every other day (Florence regimen), 38.5 Gy in 10 fractions, twice daily and 40 Gy in 10 daily fractions, amongst some others. In the present COVID-19 pandemic, a shift to APBI for eligible patients will drastically relieve the radiation service resources and there are institutions and countries releasing documents in its favor amidst the pandemic [26].

Post-mastectomy and regional nodal radiation therapy. There is an ongoing trial investigating the omission of post-mastectomy chest wall and regional nodal radiation in patients with cT1-3 N1 disease who have ypN0 status post neoadjuvant chemotherapy and surgery. However, until the results are published, the omission is not recommended outside of a clinical trial. Postmastectomy chest wall radiation can be delivered with hypofractionation in 15 fractions with non- inferior outcomes and similar toxicity [27]. There is also preliminary literature suggesting hypofractionated 15–16 fraction regimens for regional nodes. There is evidence building up even for the 5 fractionated regimen. However, with the current literature, 15 fractions are safe.

Cardiac sparing methods. Several radiation oncology centers use cardiac sparing deep inspiratory breath-hold techniques especially in left breast cancers for better cardiac sparing. There are advised caution against the use of active breathing control devices that involve the use of a mouthpiece as that involves a risk of viral transmission as the major mode of transmission is coming into contact with secretion droplets. Techniques that involve voluntary breath-hold to achieve the desired effect are recommended. Treatment in a prone position can be an option to reduce cardiac dose, though it can be a little cumbersome procedure.

Miscellaneous. Intra-operative radiation therapy can be an option as this will obviate any further need for visiting the hospital for radiation therapy. It is delivered over 20-45 minutes to the tumor bed. The surface of the bed typically receives 20 Gy that attenuates to 5–7 Gy at 1 cm depth. There are studies to support its use. Although not adopted universally in practice, it might be a very reasonable option, if available, in the COVID-19 pandemic where reduced hospital visits and social distancing is an important strategy to prevent/reduce infection.

Prioritizing of radiation therapy. Braunstein et al from MSKCC [28] has proposed an informative tier system for prioritizing radiation services in breast cancer patients during this COVID-19 pandemic. The details are shown in Table 1.

Lung cancer

In the time of the COVID-19 Pandemic, lung cancer poses a unique challenge as both the cancer and the virus predominantly

affect the lung parenchyma causing damage and respiratory symptoms. While cough and breathlessness are common symptoms of lung cancer, COVID-19 infections also present with dry cough and breathlessness commonly. As the pulmonary reserve may be affected by cancer, with the superseding risk of COVID-19 infection capable of producing severe manifestations in them, patient selection for treatment is key. Also, sequential treatments over concurrent treatments may be preferred keeping in mind the long-term goal of successful treatment completion. Management as per the stage of the disease is discussed in Table 2.

Additional points to be considered:

a) Breath hold devices are indicated in lung SBRT. As much as possible, avoid using ABC that requires a mouthpiece. Voluntary Deep Inspiration Breath Holding (DIBH) methods would be encouraged. ABC may be used for:
   i. Re-irradiation cases where the anticipated toxicity will be reduced.
   ii. Conventionally fractionated/hypofractionated or stereotactive ablative radiotherapy (SABR) plan where normal tissue constraints are not met without breath-hold technique.
b) Dose gradients recommended for stereotactive body radiation therapy (SBRT) have been given in RTOG 0915 and RTOG 0813 and these can be referred to the for the constraints described.
c) Centers with prior experience delivering lung SABR should offer single fraction SABR.
d) Tumors with movement of less than 1 cm on 4DCT imaging should be considered for SBRT.

Gynecological cancers

The following guidelines look into the potential adaptations to the evidence-based management in gynecological malignancies

Cervical cancer. External beam radiation therapy (EBRT):

- Pelvic radiotherapy with concurrent chemotherapy (wherever indicated) is still the standard of care.
- Both concurrent and systemic (cisplatin-based) chemotherapy should be used only if strongly indicated and depending on resource availability. It needs to be avoided altogether in patients over 70 years and with comorbidities.
- Carboplatin should be avoided due to higher rates of pancytopenia.
- Gross nodes should be addressed with a simultaneous rather than a sequential EBRT boost.
- Less resource-intensive techniques like weekly cone beam computed tomography verification and liberal clinical target volume / internal target volume / planning target volume (CTV-ITV-PTV) margins may have to be accepted.
- Avoid extended field EBRT as far as possible.

Brachytherapy:

- Intrauterine brachytherapy is an essential part of the treatment for cervical cancer that cannot be omitted in the curative setting.
- In resource-limited set-up, a reference to another center for brachytherapy (without severely affecting overall treatment time) is advised. When that is not feasible, consider the EBRT boost.
- An expert panel should sit together to prioritize patients according to the potential benefit of brachytherapy depending on EBRT response, age, nodal involvement and overall treatment time. A virtual tumor board through online meetings can also help make decisions.
- Another alternative is to deliver 2 or 3 fractions per insertion with a gap of at least 6 hours between fractions. In the absence of spinal or general anesthesia, small diameter applicators using a local anesthetic or mild sedation can be used for brachytherapy.
- MRI-based planning may be done at least for the first fraction, especially in bulky residual disease after EBRT requiring interstitial needles. CT based planning is acceptable for all other cases.
- Image-guided adaptive planning is preferred in gross residual disease cases at the time of brachytherapy. And simple point A based planning is good for low volume good responders.

Stage wise treatment recommendations are given in Table. 2

Endometrial cancer. External beam radiation therapy**:**

- Endometrial cancer is typically a disease of postmenopausal, elderly women, a group that is most vulnerable during this coronavirus pandemic.
- Surgery remains the mainstay of treatment for endometrial cancer. However, if most elective surgeries get canceled during the lockdown period, consider alternatives such as megestrol, medroxyprogesterone, or a levonorgestrel intrauterine device to allow surgery after a delay of a few weeks or months [46].
- Radical radiotherapy (EBRT) is an alternative option, however, much inferior in results to surgery. Very rarely, brachytherapy alone is used for early-stage disease (using a Rotte applicator). Both of these are options only in severely resource-limited setups.
- For very locally advanced disease inoperable or metastatic disease, consider chemotherapy with or without radiotherapy.
- Adjuvant radiotherapy: It may be omitted in low and intermediate-risk Stage I cases and may be delayed in the high intermediate-risk category for up to 3 months. But the high-risk Stage I and Stage II onwards or high-risk features (positive margin, type 2 histology, residual disease at stump) may warrant adjuvant EBRT and/or vault brachytherapy.

Brachytherapy:

- Vault Brachy: With EBRT: 6-8 Gy x 2 # weekly and without EBRT: 7 Gy x 3# weekly

Management of endometrial cancer as per the stage of the disease is shown in Table 2.

Vulvar cancer.

- This group of cancers is also common in elderly women making them a susceptible group for hospital acquired Covid 19 infection.
- In view of reduced surgeries during a pandemic, radical radiotherapy becomes the treatment of choice in vulvar cancers.
- Concurrent chemotherapy may be avoided in patients >70 years, poor PS, co-morbidities or immunocompromised.
- Adjuvant radiotherapy should be given to patients with positive resection margins, residual disease or 2 or more lymph node involvement (or extra capsular spread). No concurrent chemotherapy should be given.
- Radical or boost treatment with brachytherapy is not encouraged as theatres and anesthesia should be conserved for high volumes of cervix and endometrial brachytherapy.

Vaginal cancer.

- Upper vaginal cancer: Treat like cervix cancer
- Lower vaginal cancer: Treat like vulvar cancer but followed by brachytherapy

Management of vulvar and vaginal cancers is shown in Table 2.

Table 2
Management of different stages / presentations of various cancers during a pandemic

LUNG CANCER

Disease category	Recommendation in COVID-19 pandemic
NSCLC, T1/2N0M0, medically inoperable; peripheral [29,30]	• SBRT 30-34 Gy in single fraction (T1 N0M0) • 54 Gy in 3 fractions in 1.5 weeks (Eligibility includes T1, 2 (<5 cms), T3 <5 cms, chest wall involvement positive, no mediastinal or bronchial tree invasion)
NSCL, T1/2N0M0, medically inoperable, central [31]	• 48 Gy in 4 fractions, daily RT • 60 Gy in 8 daily fractions • 70 Gy in 10 daily fractions • 50 Gy in 5 daily fractions
Stage I-IIIB tumor, operated	• Short delay in radiation if R0 resection
Stage III, Locally advanced NSCLC [32]	• 55 Gy in 20 fractions with concurrent/sequential chemotherapy • 60 Gy in 15-20 fractions • (RT alone)
NSCLC, advanced- inoperable, large for curative RT [33]	• Palliative RT → 1-2 fractions of 8 to 10 Gy/fraction (weekly if 2; may be supported with sequential chemotherapy:
SCLC, localized [34,35]	• 40-42 Gy in 15 daily fractions
SCLC, Extensive [36–38]	• Omit Prophylactic cranial irradiation. • **ESTRO COVID-19 pandemic guideline also recommends** - Consider omission of consolidation thoracic radiotherapy in extensive stage disease

CERVICAL CANCER

Site of Cancer	Preferred treatment	EBRT	Brachytherapy
Stages (FIGO 2019) IB3, IIA2-IIIC2 and early IVA (focal infiltration of bladder or rectum: 1 × 1 cm)	• Radical: Radiotherapy (EBRT) + concurrent chemotherapy [39,40]	• 50.4 Gy / 28 fractions (preferred for bulkier or node positive) with 3DCRT • 45 Gy / 25 fractions with SIB to gross nodes • 55-62.5 Gy / 25 fractions) with IMRT [41,42]	• Intracavitary HDR brachytherapy 3 fractions (EQD2 of at least 85 Gy to point. A) • If theatre/anaesthesia limitations present, then consider EBRT boost (18 Gy in 10 fractions)
IA1, IA2, IB1, IB2, IIA1	• Adjuvant: EBRT + conc. CT for high risk patients (Sedlis criteria + positive nodes / parametria / margin)	• 45 Gy / 25 fractions with IMRT; if resource constraints, 3DCRT [43]	• Vault brachytherapy 6 Gy x 2 fractions where indicated
IVA (frank bladder or rectal infiltration) or IVB	Palliative • Pain • Bleeding	• 8 Gy single fraction or 20 Gy in 5 fractions [44,45]	• No

ENDOMETRIAL CANCER

Site of Cancer	Preferred treatment	EBRT	Brachytherapy
Stages IA Gr 1-Gr 3 and IB Gr 1-2	• Observation only	• No	• Vault brachytherapy if positive margins, suboptimal surgery (defer as long as possible)
Stages IB Gr 3, Stage II	• EBRT 8-12 weeks post surgery	• 45 Gy in 25 fractions (IMRT preferred) [47]	• Vault brachytherapy [can consider only brachytherapy (no EBRT) in Stage IB G3 and Stage II, G1 and G2 with no high-risk features]
Stage IIIA-IIIC	• Systemic therapy and / or EBRT 6-8 weeks post-op	• 45 Gy in 25 Fr (IMRT preferred) [48]	• Vault brachytherapy [49]
Stage IVB	• Only systemic therapy • Palliative: i)Pain ii) Bleeding	• 8 Gy single fraction • 20 Gy / 5 fractions [50]	• No
All stages	• Radical: EBRT + chemotherapy considered on a case by case basis (those unable to have surgery) [51]	• EBRT (IMRT) + brachytherapy should deliver an EQD2 D90 of 65 Gy to the uterus, cervix and upper vagina • Only brachytherapy should deliver at EQD2 D90 of 48 Gy	• Alone or in combination with EBRT

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Table 2
(*Continued*)

VULVAR AND VAGINAL CANCERS

Site of cancer or presentation	Preferred treatment in a Pandemic	EBRT	Brachytherapy
Vulva, radical	• EBRT + chemotherapy [52,53]	• 45 Gy / 25 fractions followed by 18-20 Gy / 9-10 fractions to gross disease (IMRT or VMAT only) • SIB to primary and nodes (preferred to reduce overall time)	• Best to avoid in resource-limited setting
Vulva, adjuvant	• Adjuvant: Groin and pelvic EBRT (U/L or B/L) in high risk features (mentioned in text)	• 45 Gy / 25 fractions [54,55]	• No
Vulva, palliative	• Palliative [56]: i) Pain ii) Bleeding	• 8 Gy single fraction • 20 Gy / 5 fractions	• No
Vagina, upper vagina	• Treat as cervix cancer	• Yes	• Yes
Vagina, lower vagina	• Treat as vulvar cancer	• Yes	• Yes

PROSTATE CANCER

Disease Stage	Preferred treatment	ADT (before RT)	EBRT	Brachytherapy
Very low/low risk	• Active surveillance and repeat PSA after 6 months	• No	• No [59]	• No
Favourable Intermediate risk	• Active surveillance and repeat PSA after 3-6 months	• No	• Delay until safe [59]	• Delay until safe
Unfavourable Intermediate risk	• ADT + RT	• 4-6 months (up to 8 months also if safe) [60]	• Modest hypofractionation (60 Gy/20 fractions) • Ultra hypo-fractionated regimens: - 42.7 Gy/7 fractions every other day - 36 Gy/6 fractions/6 weeks. • 5 fraction stereotactic body radiotherapy (SBRT) (most preferred) if good planning and delivery possible [61–64]	• Delay until safe
High/very high risk	• ADT + RT	• 2-4 months		• Delay or avoid
N+	• ADT + RT • [65]	• 2-4 months		Not recommended
Adjuvant RT	• Early salvage (consider strongly) over adjuvant RT ± ADT [66,67]	• 4-6 months	• Standard (33-35 fractions) • Hypofractionation (60 Gy/20 fractions) if high risk features on HPR Note: Attempt to defer RT in all cases with use of ADT]	• -
Oligometastatic	• ADT + RT [68]	• 2-3 months	• SABR though popular has less survival benefit (1 fraction or 3 fractions) Note: Needs to be discussed in resource limited setting and deferred as much as possible	• -
Low volume M1	• ADT + prostate-directed therapy [69,70]	• 4-6 months	• 5 or 6 fractions Note: Needs to be discussed in resource limited setting and deferred as much as possible	• -

GI MALIGNANCIES

Esophageal malignancies
1. If neo-adjuvant chemoradiotherapy considered → 40 Gy in 15 fractions with concurrent chemotherapy (carboplatin and paclitaxel) [74]
2. Induction chemotherapy can result in increased in immunosuppression adding to the risk of infection
3. Definitive chemoradiation therapy can be considered as the best curative option with carboplatin and taxol based chemotherapy because of lower toxicity [75]. If tumor 5 cm in length → 50 Gy in 16 fractions and if up to 10 cm → 50-55 Gy in 20 fractions [76]
4. Consider delaying adjuvant therapy for up to 12 weeks

Locally advanced unresectable pancreatic cancers
1. Hypofractionated radiation therapy (45 Gy in 15 fractions) with concurrent capecitabine
2. A hypofractionated regimen of radiation therapy (25-35 Gy in 5 fractions) [77]
3. Radiation therapy needs to be avoided if the direct invasion of bowel and stomach is observed

Rectal cancer
1. Long course treatment for threatening margins should be converted to short course treatments (avoid in young, fit patients) [78]
2. Avoid short course if significant pelvic disease present
3. 25 Gy/ 5 daily fractions [79]
4. Surgery can be delayed up to 8 weeks [80]

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Table 2
(*Continued*)

SOFT TISSUE SARCOMA 1. Standard pre-operative radiotherapy needs to be discontinued during the pandemic 2. Consider surgery as the first line for local management 3. Role of protracted radiotherapy regimens: if pre-operative radiation is being considered → 25 Gy in 5 fractions can be considered if the disease is not close to critical structures followed by surgery after 1-2 weeks [97] 4. If radiation therapy facilities are restricted due to COVID-2019, the treatment can be deferred and started within a reasonable time frame and if no local recurrences have developed 5. In some patients, hypofractionated dose schedules of 40-45 Gy in 15-20 fractions and 36 Gy in 6 once weekly fractions can be considered, except in young patients due to increased late radiotherapy related toxicities [98] 6. In other forms of sarcoma → . Radiation therapy can be deferred in view of restricted radiation therapy delivery and individual case-based decisions need to be taken
UROTHELIAL MALIGNANCIES 1. For T2-T4 N0M0 disease - Radical radiation therapy with 55 Gy in 20 fractions can be considered with weekly gemcitabine [99] 2. Palliative radiation therapy schedules: • 21 Gy in 3 fractions [100] • 36 Gy in 6 fractions given weekly [101] • 8-10 Gy in single fraction for bleeding or local symptom control
PEDIATRIC MALIGNANCIES 1. CNS tumors including medulloblastoma, grade 2/3 ependymoma, embryonal CNS tumors, intracranial germ cell tumors, atypical teratoid/ rhabdoid tumor → Delay in radiation therapy can lead to poor survival outcomes and need to be treated on priority basis 2. Similarly, total body irradiation, retinoblastoma, nasopharynx and head and neck malignancies require priority for treatment with radiation therapy 3. Adjuvant therapy can be considered as a priority in cases where tumors present with an aggressive histopathology or residual disease which could lead to deteriorating symptoms
THYROID 1. A delay in radioactive iodine treatment will not impact the prognosis in differentiated thyroid cancer (DTC) 2. Metastatic disease → Treatment decisions can be made based on the risk-benefit assessment on an individual basis
NON-MALIGNANT LESION AND SKIN TUMORS 1. Suspend all treatment forms until the pandemic is over
PALLIATIVE RADIATION THERAPY
Brain metastases 1. Keep the patient visit and duration of stay in the hospital as brief as possible 2. For metastases <10cc → consider single fraction treatment 3. If SRS is a feasible option, it can replace neurosurgical options where resources are deemed limited [81] 4. Postoperative: SRS to the cavity → 5 Gy in 7 fractions [82–84] 5. If life expectancy >3 months → 4 Gy in 5 fractions to whole brain [85] 6. Poor performance status → Best supportive care with review for the need of steroids [86]
Spinal cord compression (SCC) 1. Assess for extent of spinal cord compression, presence or absence of spinal cord instability → 8 Gy in single fraction [87]
Tumor bleeding 1. 'Quad-Shot' regimen → 3.7 Gy x 4 fractions twice daily, 3 weekly, 3 courses [88] 2. 4 Gy x 5 fractions given daily [89] 3. Single fraction of 8Gy [90] 4. Twice daily treatment is not recommended during a pandemic
SVC syndrome 1. 8.5 Gy x 2 fractions, a week apart [91] 2. 4 Gy x 5 daily fractions [92] 3. 8-10 Gy in single fraction [93–95]
Painful bone metastases 1. Consider all medical strategies and supportive care before offering radiation. 2. In patients with impending fracture, discuss the option of mechanical stabilization with orthopedic surgeon and interventional radiologist 3. 8 Gy single fraction [96]

Genitourinary cancers
Prostate cancer.

- Compared to other cancers in India, prostate cancer is not a heavy burden on radiotherapy departments. Generally, it has a more favorable prognosis and is responsive to androgen deprivation therapy (ADT) which allows a safe delay of radical treatment for many months. This helps to reduce the overall burden on the system and staff considerably. Thus, it is possible to divert resources to more urgent needs during the COVID-19 pandemic.
- Fiducial application and rectal spacer application must be considered only if performing SBRT.
- If ADT is initiated consider 6-month depot injection, in which case radiotherapy can be delayed for up to 4–6 months (in low-risk cases, even for up to 8 months).
- If ADT cannot be delivered (eg, patient refusal, cardiac toxicity) and there is a rapid Prostate Specific Antigen (PSA) doubling time (≤3 months) the benefits of starting RT must be weighed against COVID-19 exposure and subsequent morbidity and mortality especially in the aged with multiple co-morbidities or in the immunocompromised.
- Hypofractionation with 5 fractions (preferred) or 20 fractions should be established as the new normal during this phase.
- Brachytherapy is to be avoided as far as possible as the availability of theatres and anaesthesiologists are limitations.
- If pelvic nodes are to be treated, opt for a hypofractionated schedule (60 Gy/20 Fr) with uninvolved nodes receiving 42-44 Gy in 20 fractions [57,58].
- Further stage-wise management is described in Table 2.

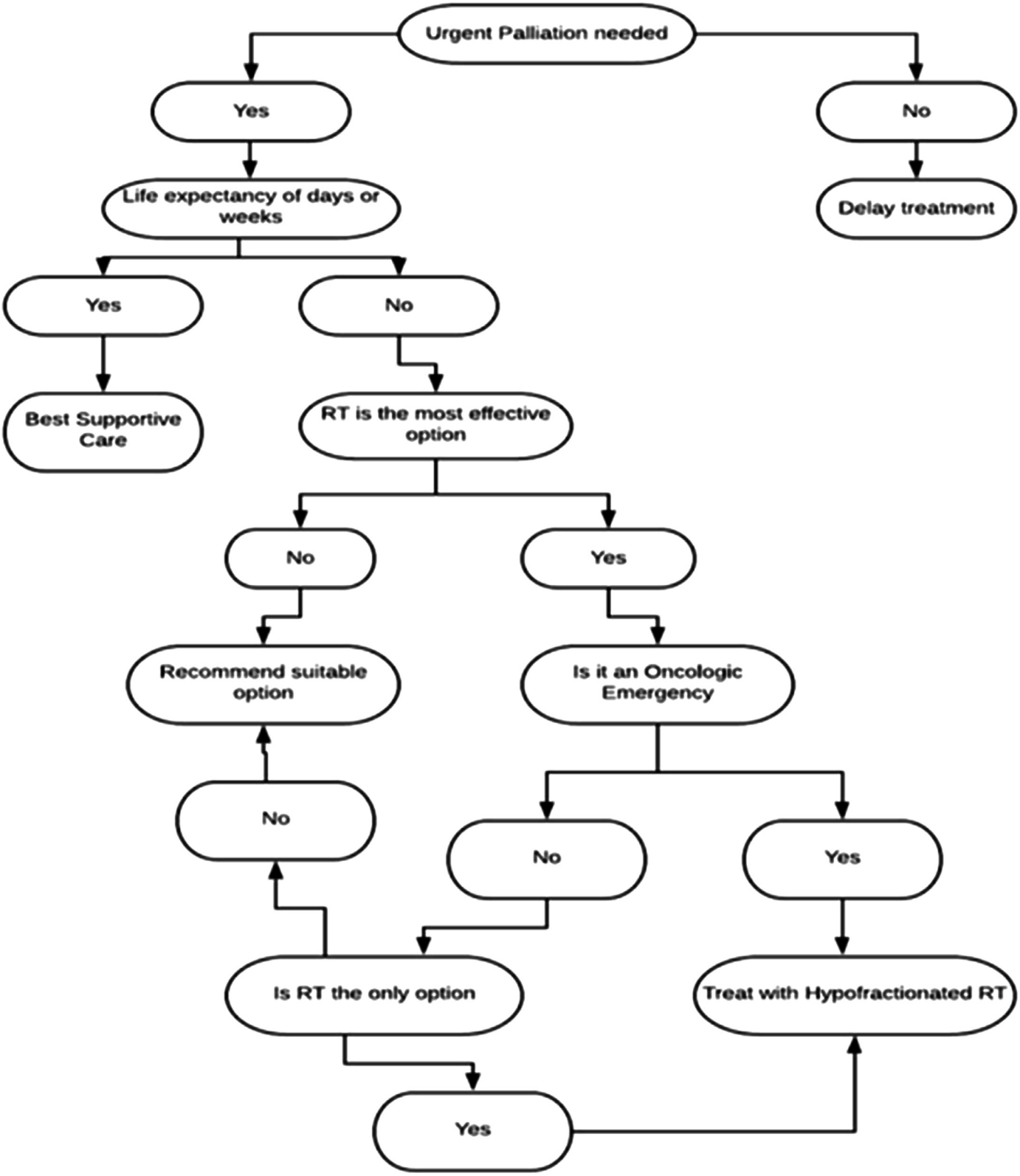

Fig. 5. Algorithm for management decisions for palliative treatment during COVID-2019.

Also, note that in centers where brachytherapy of prostate is commonly done,

- Convert all HDR monotherapy cases (2 implants) to HDR boost (single implant 15 Gy in 1 Fr) if the operation theatre resources permit. If not, convert to EBRT or commence ADT.
- EBRT schedules that are due for HDR boosts (15 Gy in 1 Fr) can be converted to 37.5 Gy/15 fractions.

Seminoma: Rarely treated with RT. Even in Stage 1, favor surveillance [71]

Renal cell carcinoma. Primary and metastatic RCC are typically treated with SABR, mostly under the trial setting. All cases require thorough discussion. Defer cases where it is deemed possible to perform active surveillance. If treatment is warranted urgently, and suitable resources are available, a single fraction SABR may be given [72,73].

Gastrointestinal malignancies

The spectrum of GI malignancies encompasses various disease sites and the best available treatment options are discussed in Table 2.

Palliative radiation during pandemic

Palliative radiation has a crucial role in the prevention of serious morbidity, palliation of bothering symptoms and also in the setting of oncologic emergencies. Estimated benefits and prognosis should be communicated to the patients, including the risk-benefit analysis. Patients who are well prognosticated regarding their disease, avoid aggressive treatment near the end of life and usually opt for medical supportive care. The use of abbreviated RT courses may reduce hospital visits and therefore the risk of exposure.

Concerns associated with treatment.

- Radiation needs daily hospital visits, thus a higher risk of exposure to infection. Exposing fragile patients to this risk for palliative treatment needs risk-benefit analysis.
- Patients with a life expectancy of days to weeks should be offered best supportive care.
- Disease extent, palliative intent of treatment, available treatment options, the benefit of each option is to be explained to patients and care-givers.
- Patients receiving palliative treatment usually need support for mobilization and positioning for different procedures. A higher number of caregivers is needed, with a higher risk of transmission. The number of visitors should be kept to a minimum.
- Patients receiving palliative treatment are at a higher need for in-hospital admissions due to their limited mobility or continuous need for medical attention. They should be offered options that reduce their hospital stay or hospital visits.
- Treatment options should be chosen after considering the benefit obtained from a particular modality, hospital stay required, along with the chances of contact with another individual.

Management of Oncologic Malignancies: The various oncological emergencies and palliative radiation therapy needs are covered in Table 2 and an algorithm for management decisions in palliative oncology have been depicted in Fig. 5.

Prioritizing treatment options in miscellaneous sites: We have summarized the various subsites of oncology and the required management of malignancies which do not form the bulk of patient load in the regular radiation oncology department but when faced with, can be challenging to treat in a pandemic. Table 2 presents the details related to the treatment options and the available evidence.

Conclusion

Over the next few months, we as oncologists will see a major change in the management strategies as long as the pandemic lasts and along with the best available treatment options, counseling of the patient will also take center stage. It is vital to explain to patients the benefit of radiotherapy balanced against the accepted risk associated with contracting COVID-19 during the treatment period. These new protocols will have to be accepted as the "new normal" and set in place as there is a high likelihood that the pandemic may last for several months. We have attempted to bring together guidelines from all over the world under one roof to help clinicians make a well-planned decision related to radiation therapy. The guidelines are ever-evolving and the structured plans depicted in the article may change with potential developments in the future.

Conflict of Interest

None.

Disclosure

None of the authors have any disclosures to declare

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