Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 Rapid Letter

Hypofractionation in COVID-19 radiotherapy: A mix of evidence based medicine and of opportunities ☆

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Since January 2020, the spread of the COVID-19 pandemic in China and, in the next weeks, in Italy and then in the rest of Europe and the world, has had an enormous impact on the organization, safety procedures and prescription behavior of the physicians in radiation oncology. The main concerns expressed in the numerous comments, letters and papers published in the last three months are (a) how to assure the normal supply of the radiotherapy treatments; (b) how to keep constant the number of Healthcare Workers (HCW); (c) how to identify radiotherapy (RT) patients SARS-CoV-2 positive; (d) how to protect HCW from the viral infection; (e) how to protect the patients from the infections; (f) how to reduce the postponing and the delay of RT start.

In previous communications, the initial modifications of the clinical activity in a radiotherapy department in Southern Italy – an area with a relative of low incidence of infections – were described soon after the declaration of the pandemic [1] and some criticism were addressed towards the safety recommendations of the national governmental and the scientific institutions, as they were contradictory and arguably inadequate to ensure patients' and HCWs' safety [2]. Many papers have been published with the aim to resume the Hypofractionated (HF) schedules which are considered more suitable for avoiding many visits to the hospital centre, for respecting the time between surgery and RT and thus reducing the risk of infection. Last 29 April, a search on Pubmed (www.pubmed.gov) based on the query radi*otherapy + covid-19* gave 53 papers. Among these, we selected those regarding fractionation scenario. In Table 1, the HF schedules proposed in this pandemic period, from different countries, are summarized [3–14]. They are well known schedules, already used with different *motivations*: (a) short life expectancy or poor general conditions; (b) advanced age and logistic problems in reaching the RT hospital; (c) radiobiological evidence in tumors with higher sensitivity than conventional fraction dose (breast, prostate); (d) the need to reduce inpatient stay for palliative treatments; (e) the increasing demand of >RT, in countries with universal access to health services, produced a relative shortage of machines and an increasing of waiting times.

Evidence-based decisions are a cornerstone also in medical sciences, at least at theoretical; its matching in the practices is however, sometimes, difficult to detect. For instance, point e) of the motivations for prescribing HF schedules, in Italy it is difficult to find it in a private setting (also when the private structure supplies radiotherapy on behalf of Health Public Service (HPS)) because reimbursement is on daily session basis. Recently, in the era of dynamic conformational techniques, the use of HF schedule has become more diffuse, also in the private structures, because they obtain in some region – the HPS is regional in Italy – a better reimbursement. During a pandemic, it may happen the occurrence of fault lines in medicine. One of these is the "willingness on the part of clinicians to abandon the *prime dictum* of medicine, to do no harm, and rush into treatments that not only may be useless but may well be dangerous. [15] The fact is, most physician are not trained to recognize good science from bad. Nor do they have the time to analyze every study, and too many are willing to ignore the need for reliable evidence when fear sets in" [16]. Are we going to his pitfall?

Some fractionations in Head & Neck tumors, in a scenario where the RT resources are severely reduced, are quite anecdotic and based only on the consensus and preference of the physician [3]. While for breast [5], in stage I NSLC [4], rectum [8,9], prostate [11], the schedules are supported by clinical trials, for some other schedules, such as some palliative one in glioblastoma [10] or whole breast over 70-year [12], their efficacy is still to be proved.

At the onset of the pandemic, many treatments were postponed by the patients themselves or by the RT departments to minimize the number of the visits in the RT centers to the urgent and binding cases [1]. So this decision could have theoretically impacted on the outcomes of some treatments. HF RT should be delivered only where solid scientific evidence is available, while some shortest courses in palliative setting likely are unuseful and therefore it would be better to deny them. In a palliative setting, the pandemic will allow us, perhaps, to avoid inappropriate therapy to some patients.

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Table 1
Resume of HF schedules suggested during Covid-19 pandemic. Abbreviations: PBI: partial breast irradiation; WBRT: whole breast irradiation; PMRT: post mastectomy radiotherapy; RNI: regional node irradiation; SIB: simultaneous integrated boost; NSCLC: non small cell lung carcinoma; SBRT: stereotactic body radiotherapy; CRM: circumferential resection margin; TME: total mesorectal excision; SCRT: short course radiotherapy; HL: Hodgkin Lymphoma; NHL: Non-Hodgkin Lymphoma; NK-T: natural killer-T; H&N: head and neck; IR-HR: Intermediate and High risk; WBRT: whole brain radiotherapy; BID: twice daily; GBM: glioblastoma multiforme; SVC syndrome: superior vena cava syndrome; TMZ: temozolomide; IORT: intraoperative radiotherapy; HPV: human papilloma virus; KPS: Karnofsky performance status; SRS: stereotactic radiosurgery; DCIS: ductal carcinoma in situ; SCLC: small cell lung carcinoma.

Author (ref)	Country	Site/General	Fractionation schedules
Thomson [3]	International	H&N	Scenario 1-early COVID-19 pandemic-risk mitigation: agreement use of conventional or midly hypofractionated radiotherapy with concomitant chemotherapy: (52%: 2–2.2 Gy/f, 21% 2.2–2.4 Gy/f, 24% 2.4–2.6 Gy/f, 3% 2.6–2.8 Gy/f) palliative RT: 30 Gy/10f (17%), 44.4 Gy/12f (17%), 20 Gy/5f (13%), 32 Gy/4f (7%) 8 Gy/1f (4%) Scenario 2-later COVID-19 pandemic -severely reduced RT resources: hypofractionation is strongly recommended. Oropharinx p16 neg pT2N2bM0: 2.14–3 Gy/f (70%) Larynx T1bN0M0 (glot): 2.41–3.2 Gy/f (70%) Larynx T3N1M0: 2.21–2.8 Gy/f (80%) Hypopharinx palliative: various- 8 Gy/1f 20 Gy/5f
Braunstein [4]	NY-USA	Breast	PBI: 30 Gy/5f every other day (preferred) or daily (acceptable) or 40 Gy/10 daily WBRT: 26 Gy/5 daily +/- 5.2 Gy × 1 boost or 40 Gy/15 daily or 42.4 Gy/16 daily PM-RT: 42.56 Gy/16f BREAST AND RNI: 42.56 Gy/16f with SIB on tumor bed 48 Gy/16f or 40 Gy/15f with SIB on tumor bed 48 Gy/15f
Coles [5]	International	Breast	WBRT, node negative: 28–30 Gy/5f (weekly) or 26 Gy/5f (daily) (FAST and FAST Forward trials, respectively) WBRT, node positive: 40.05 Gy/15f PBI: 28.5–6 Gy/5f (over 1–2 weeks)
Guckenberger [6]	Europe/USA	Lung	*NSCLC Stage I:* 45–54 Gy/3f or 48 Gy/4f (standard) or 30–34 Gy/1f *NSCLC Stage III:* Exclusive RT: 60 Gy/15–20f or 60–66 Gy/24–30f or 55 Gy/20f Sequential RTCT: 60–66 Gy/24–30f or 55–60 Gy/20f or 60 Gy/15f *Palliative NSCLC:* 30 Gy/10f (standard) or 20 Gy/5f or 17 Gy/2f or 8–10 Gy/1f (strong recommended)
Tchelebi [7]	USA, Europe	GI	*Esophagus:* definitive RT followed by CHT: 40 Gy/15f definitive exclusive RT: 50 Gy/16 or 20f palliative RT: 30 Gy/10f or 6–8 Gy/1f (pain or bleeding) or 20 Gy/5f (dysphagia) *Stomach:* palliative RT: 6–8 Gy/1f *Liver:* 16–30 Gy/1–3f or 48–60 Gy/3–5f (SBRT) *Cholangiocarcinoma:* 67.5 Gy/15f or 30–60 Gy/3–6f (post induction CHT) *Pancreas:* Bordeline resectable: 30–33 Gy/5f (SBRT) or 25 Gy/5f or 30 Gy/10f with concurrent gemcitabine Inoperable: 30–40 Gy/5f (in case of response post CHT) *Rectum:* locally advanced operable: preoperative 25 Gy/5f (after induction CHT) inoperabile: 52 Gy/20f
Romesser [8]	NY-USA	Rectum	Locally advanced (also low-located, close CRM): 25 Gy/5f (SCRT) delay surgery
Marijnen [9]	International	Rectum	ESMO rectal cancer guidelines Intermediate group (if good TME cannot be assured): 25 Gy/5f (SCRT) Locally advanced rectal cancer: 25 Gy/5f (SCRT delay surgery) Advanced group: pre-operative CRT or 25 Gy/5f (SCRT followed by neo-adjuvant chemotherapy)
Yahalom (ILROG) [10]	International	Hematological malignancies	HL favorable chemosensitive: 18 Gy/6 f HL unfavorable chemosensitive: 27 Gy/9 f HL chemorefractory: 36-39 Gy/12-13 f } Only in critical resource shortage situation Aggressive NHL,chemosensitive: 25 Gy/5f or 27 Gy/9f Aggressive NHL,chemorefractory: 30 Gy/6f Localized aggressive NHL, exclusive RT: 36–39 Gy/12–13f Indolent lymphoma, limited stage: 4 Gy/1f or 20 Gy/5f NK/T-cell lymphoma: 36 Gy/9f Cutaneus T cell lymphoma: 8–12 Gy/2–3f Solitary bone plasmocitoma or solitary extramedullary plasmocitoma: 30 Gy/6f (non spine/H&N site) and 36 Gy/12f (spine/H&N site) Palliation: symptomatic aggressive: 25 Gy/5f

Table 1 (*continued*)

Author (ref)	Country	Site/General	Fractionation schedules
Zaorsky [11]	USA-UK	Prostate	IR/HR localized: 5 to 7f (SBRT) (v. 2020 NCCN guidelines) or 60–62 Gy/20f post-prostatectomy: 52.5 Gy/20f oligometastatic: 1 or 3 fractions (SBRT) low volume M1: 3–5 fractions (SBRT) or 36 Gy/6f (STAMPEDE)
Simcock [12]	USA, UK, Italy	General	Palliation: painful bone metastases (no fracture) +/− spinal cord compression: 6–10 Gy/1f bone metastases (fracture/surgery): 20 Gy/5f brain metastases (SRS) 15–20 Gy/1f palliative WBRT: 20 Gy/5f palliative WBRT (poor prognosis): 12 Gy/2f esophageal bleeding/dysphagia: 12 Gy/4f (BID) or 15 Gy/3f or 18 Gy/3f (day 0,7,21) GBM (poor prognosis): 25 Gy/5f Palliative H&N: 30–36 Gy/5–6f (2f/week) Palliative H&N: 18–24 Gy/3f (day 0,7,21) SCV syndrome/lung cancer: 8–10 Gy/1f or 17 Gy/2f (1 week) Low grade Lymphoma: 4 Gy/1f Pelvic/GI bleeding 20–24 Gy/5–6f or 18 Gy/4f (BID) or 14,8 Gy/4f (BID) (repeatable for a total dose of 44.4 Gy, in 3 courses) or 18–24 Gy/3 (Day 0,7,21) Radical RT:*GBM* (age > 65): 40.05 Gy/15f + TMZ *Bladder* (cT2-4aN0,RTCT): 55 Gy/20f *Breast:* PBI-early stage: 30 Gy/5f or 38.5 Gy/10f (BID) PBI-early stage (IORT): 20 Gy/1f WBRT, N0-early stage: 28.5 Gy/5f WBRT, +/- LN-early stage: 26 Gy/5f WBRT, + LNs: 40.05 Gy/15f Chest wall: 40.05 Gy/15f or 43.5 Gy/15f Whole breast/Chest wall (>70y): 30–37.5 Gy/6f (weekly) *H&N*: HPV + definitive-localized: 60 Gy/30f Definitive: 66 Gy/33f (6f/week) *Lung:* N0, medically inoperable (T1-T2, peripheral): 30–34 Gy/1f or 54 Gy/3f (SBRT) Locally advanced NSCLC (conc RTCT): 55–57.5 Gy/ 22–23f NSCLC (sequ RTCT): 54–60 Gy/ 18–20f NSCLC N+ (exclusive RT): 60 Gy/15f SCLC (RTCT): 40.05–42 Gy/15f *Pancreas:* locally advanced: 25–50 Gy/5f *Prostate:* any risk: 60 Gy/20f IR-HR, prostate only: 42.7 Gy/7f LR-IR, prostate only: 36.25–40 Gy/5f (SBRT) HR or M1 (>75y or 70y with comorbidities): 36 Gy/6f Post-prostectomy, fossa only: 52.4 Gy/20f or 62.5 Gy/25f *Rectum:* cT3-4 preop-RT: 25 Gy/5f
Combs [13]	Germany	General	*GBM* KPS 100–80; >60-65y: 40.05 Gy/15f + TMZ KPS < 60; 25 Gy/5f (no TMZ) *Brain Metastases* 1–10 mts: good KPS: 18–20 Gy/1f (SRS) Post op: 35 Gy/7f or SRS Life expectancy > 3 months: 20 Gy/5f (WBRT) Meningeoma: WHO 1: 25 Gy/5f *Breast* DCIS: 40.05 Gy/15f (omit RT in case of low risk) Invasive: 40.05 Gy/15f or 26 Gy/5f (omit RT in case of low risk) N+: 40.05 Gy/15f Postmastectomy (Hypofractionation if not implant): 40.05 Gy/15f or 43.5 Gy/15f PBI: 38.5 Gy/10f (BID) or 30 Gy/5f or or 28.5 Gy/5f (weekly) or 26 Gy/5f (daily) PBI (IORT): 20 Gy/1f *Lung* NSCLC stage I: 45 Gy/3f or 60 Gy/8f or 34 Gy/1f NSCLC stage III: 66 Gy/24f SCLC limited stage: 40.05 Gy/15f *Prostate* IR/HR: 60 Gy/20f IR/HR < 75y:42.7 Gy/7f Adjuvant/salvatage: 52.5 Gy/20f *Palliative RT:*

(*continued on next page*)

Table 1 (*continued*)

Author (ref)	Country	Site/General	Fractionation schedules
			bone mets: 8 or 10 Gy/1f or 20 gy/5f or 21 Gy/3f H&N: QUADshot:14 Gy/4f (BID), Q4 weeks interval x2 times bleeding: 8 Gy/1f oligometastatic: SBRT (1–5f)
Yerramilli [14]	USA	Palliation	*Brain metastases:* WBRT: 20 Gy/5f *Cord compression:* 8 Gy/1f *Tumor bleeding:* 14.8 Gy × 4f (BID) or 20 Gy × 5f *SVC syndrome/Airway Obstruction* 17 Gy/2f (weekly) or 20 Gy × 5f *Bone metastases:* 8 Gy/1f

Another aspect regards the patient's consciousness. About ten years ago, when we started HF schedule of 15 fractions, after a breast conservative surgery with the publication of START trials [17,18], a strong argue with a patient occurred because she was concerned that our proposal to shorten the treatment time was due to the willingness to reduce the waiting times, rather than to work more and harder to treat all patients with the best schedules. It is now more frequent to meet patients who ask us to be treated in 5 fractions [9].

"Therefore, efforts should focus on making healthcare professionals, more sensitive to the limitations of the evidence, training them to do critical appraisal, and enhancing their communication skills so that they can effectively summarize and discuss medical evidence with patients to improve decision-making" [15].

We hope that the pandemic will not lead us to join to HF schedules uncritically, driven only by the urgency of the moment and let us time to discriminate what is solid and what is weak. The need of respecting the timing [19] cannot be harmful for our patients and the lack of administrative support by means of delivery of adequate protections and timely staff recruitment cannot be changed by bad RT treatments.

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References

[1] Portaluri M, Tramacere F, Portaluri T, Gianicolo ELA. Southern Italy: How the supply of radiation therapy, patient outcomes, and risk to health care providers have changed during the COVID-19 pandemic. Adv Radiat Oncol 2020. https://doi.org/10.1016/j.adro.2020.03.016.
[2] Portaluri M, Bambace S, Tramacere F, Errico A, Carbone S, Portaluri T. Staff and patients protection in radiation oncology departments during covid-19 pandemic https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/COVID-Portaluriet-al-2(ADRO).pdf.
[3] Thomson et al. Practice recommendations for risk-adapted head and neck cancer radiotherapy during the COVID-19 pandemic: an ASTRO-ESTRO consensus statement. Int J Radiat Oncol Biol Phys 2020.
[4] Braunstein et al. Breast radiation therapy under COVID-19 pandemic resource constraints-approaches to defer or shorten treatment from a comprehensive cancer center in the United States. Adv Radiat Oncol 2020.
[5] Coles et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. Clin Oncol 2020;32:279–81.
[6] Guckenberger et al. Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: an ESTRO-ASTRO consensus statement. Radiother Oncol 2020;146:223–9.
[7] Tchelebi et al. Recommendations on the use of radiation therapy in managing patients with gastrointestinal malignancies in the era of COVID-19. Radiother Oncol 2020;148:194–200.
[8] Romesser et al. Management of locally advanced rectal cancer during the COVID-19 pandemic: a necessary paradigm change at memorial Sloan Kettering Cancer Center. Adv Radiat Oncol 2020.
[9] Marijnen et al. International expert consensus statement regarding radiotherapy treatment options for rectal cancer during the COVID 19 pandemic. Radiother Oncol 2020;148:213–5.
[10] Yahalom et al. ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic. Blood 2020.
[11] Zaorsky et al. Prostate cancer radiotherapy recommendations in response to COVID-19. Adv Radiat Oncol 2020.
[12] Simcock et al. COVID-19: Global radiation oncology's targeted response for pandemic preparedness. Clin Transl Radiat Oncol 2020;22:55–68.
[13] Combs et al. First statement on preparation for the COVID-19 pandemic in large German Speaking University-based radiation oncology departments. Radiat Oncol 2020.
[14] Yerramilli et al. Palliative radiotherapy for oncologic emergencies in the setting of COVID- 19: approaches to balancing risks and benefits. Adv Radiat Oncol 2020.
[15] Joannidis JPA, Stuart ME, Brownlee S, Strite SA. How to survive the medical misinformation mess. Eur J Clin Invest 2017;47:795–802.
[16] Lenzer J, Brownlee S. Pandemic science out of control. Issues Sci Technol 2020.
[17] START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, et al., The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. Lancet. 2008;371:1098-107.
[18] START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008;9:331-41.
[19] Nagar H, Formenti SC. Cancer and COVID-19 — potentially deleterious effects of delaying radiotherapy. Nat Rev Clin Oncol 2020. https://doi.org/10.1038/s41571-020-0375-1.