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Radiation treatment for adult rare cancers: Oldest and newest indication

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ABSTRACT

Aim: Aim of this analysis is to review the role of RT in the management of several rare tumors for adult patients.
Methods: Collection data regarding RT and rare tumors was made by Pubmed.
Results: For mucosal melanomas, RT is prescribed, being associated with lower local recurrence rate. For trachea tumors, RT was used as adjuvant or salvage treatment for unresectable disease. For pNET, RT can be a suitable option for post-surgical or unresectable/borderline. For bronchopulmonary neuroendocrine tumors the role of adjuvant treatments is uncertain. For hepatobiliary and ovarian malignancy, stereotactic body RT (SBRT) is a promising approach. For soft tissue sarcoma, perioperative treatments are indicated, and a growing role of SBRT in oligometastatic disease is recognized. For endocrine tumors, adjuvant RT has demonstrated benefits through reducing recurrence risk.
Conclusion: The radiotherapy is a frequent indication in adult rare cancers; thus the role of Radiation Oncologist must not be neglected.

1. Introduction

The definition of a rare cancer type is based on its incidence, even if an accepted cut-off does not exist. EU defined rare cancers as those with a prevalence of less than 6/100,000 persons per year (Aymé and Rodwell, 2014).

The National Cancer Institute (NCI), instead, defines a malignancy with a frequency inferior to 15 cases per 100,000 individuals per year as rare condition (Sharifnia et al., 2017). Based on this definition, only 11 adult cancer types are common in US (including prostate, breast, lung, colon, uterine, bladder, rectum), and 25 % of adult tumors and all pediatric cancers are considered rare (Greenlee et al., 2010; Ward et al., 2014). To date, the proper treatment approach for rare cancer types is lacking and the low incidence rate is the main barrier to the research improvement in this setting. As reported by Sharifnia et al. (2017), the differences between common and rare cancers are best represented by the availability of high level of evidence interventions (LoE). For example, for breast and prostate cancer over 20 high LoE interventions exist, while, no one exist for chordoma or chondrosarcoma (Sharifnia et al., 2017). Rare tumor knowledge is often based on case report or small size retrospective analyses (Tomich et al., 2017; Chiumento et al., 2011; Karatayli-Ozgursoy et al., 2016; Fiorentino et al., 2017). However, the role of radiotherapy (RT) as a treatment approach for cancers is established, providing good results in terms of overall survival (OS) and tolerance. Moreover, in the present scenario of robust data missing, the scientific advances in RT, including modern techniques, provide an increasing in the utilization of RT also in this setting.

Thus, based on the present background, aim of this narrative analysis is to review the role of RT in the management of several rare tumors, although limits of most studies considered are that they are

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retrospective, heterogeneous and with a limited number of patients. Such studies include different histologies and even less aggressive subtypes in patients not treated with RT.

2. Mucosal melanoma

Mucosal Melanoma (MM) is a rare disease mainly occurring in the upper aero-digestive tract and it is characterized by a poor prognosis. The vast majority of MM are diagnosed in the nasal cavities or in the paranasal sinuses while a minority arises in the oral cavity. MM occurring in the sinonasal cavities are usually confined in their primary site; on the contrary, oral cavity MM present more frequently a neck nodal involvement (Green et al., 2017). A recent retrospective National Cancer Database review analyzed more than 1800 patients with sinonosal MM and identified the following prognostic factor associated with lower survival: age, advanced stage and presence of distant metastases (Ganti et al., 2020). RT is mainly prescribed in the adjuvant setting, being associated with lower local and neck recurrence rate (Moreno et al., 2010; Saigal et al., 2012; Christopherson et al., 2015). Conventional fractionation is the most adopted treatment schedule (at 2 Gy/fraction to a total postoperative dose of 60–66 Gy); hypofractionated schedules have also been reported especially in patients being irradiated on the neck (Ballo et al., 2003; Sas-Korczynska et al., 2018). In cases of unresectable/locally advanced disease, RT has been adopted with a radical intent by several authors, who historically utilized brachytherapy, external photon/electron beam RT as well as intraoperative RT (IORT). These quite dated experiences reported encouraging data regarding local control, but median follow-up was relatively short (e.g. less than 12 months) (Harwood and Cummings, 1982; Combs et al., 2007). Due to its intrinsic high linear energy transfer (LET), Carbon Ion Therapy appears to be a promising approach when treating a radioresistant disease such as MM. A retrospective experience in 85 patients with inoperable disease treated in 1997–2006 with the exclusive Hadron carbon ion therapy and doses between 57.6–64 Gy (relative biological effectiveness, RBE) in 16 fractions, showed that the 5-year local control rate was 75 %, without late Grade III toxicity and minimal (<3%) Grade II toxicity (Mizoe et al., 2012). Another large experience involving 260 patients affected by MM and treated with Carbon Ion Therapy (median dose 57.6 Gy RBE, 16 fractions) reported a 2-year overall survival and local control rates of 69.4 % and 83.9 %, respectively. Grade 3 and grade 4 late morbidities were observed in 27 and 7 patients (Koto et al., 2017). Particular attention must be given to the concurrent use of RT and BRAF inhibitors as severe skin toxicity has been reported (Anker et al., 2016). The recent arising of immunotherapy for the treatment of cutaneous and mucosal melanoma has recently changed the therapeutic landscape of this historically lethal disease (Domingues et al., 2018). Furthermore, some studies have described how there is a synergy between radiation treatment and immunotherapy by combining the intrinsic power of radiation therapy to elicit a specific immune response directed against the tumor with a modern, highly compliant and precise dosage and the systemic activity of the drug (Loi et al., 2017; Kato et al., 2019a, b; Shoushtari et al., 2016), as recently reported in a case of an inoperable MM patient in whom a palliative course of RT (30 Gy in 10 fractions) associated with nivolumab was able to evoke a systemic response to treatment.

3. Trachea tumor

Primary tracheal cancer is a rare disease which accounts only 2% of upper airway tumors (Bhattacharyya, 2004). Of these, 75 % are squamous cell carcinomas (SCCs) and 15 % are adenoid cystic carcinomas (ACCs) (Honings et al., 2009). Other less frequent histologies are: carcinoid, lymphoma, melanoma, mucoepidermoid carcinoma and sarcoma (Madariaga and Gaissert, 2018). Tumor extension into the thyroid gland and lymphatic invasion are the main prognostic factors, whereas keratinization, dyskeratosis, necrosis and tumor thickness did not predict prognosis. ACCs resemble the well differentiated, slow-growing tumors of the salivary glands and may infiltrate the surrounding tissues, resulting in a high probability of having positive margins to surgery (Gaissert et al., 2006). In a retrospective study of SEER database (He et al., 2017), a total of 287 cases were included and median survival was 57 months. Patients were categorized as Extension1 to 4 (E1−4) and N0-N3. The 3-year survival rates of each T category were 74.7 %, 57.3 %, 28.1 %, and 9.1 %, respectively. In multivariate analysis, they noticed that age, histology, tumor size, and extension were independent prognostic factors. Surgical resection is the only curative treatment for ACC, and most articles have focused on the surgical outcome. RT was used as an adjuvant treatment for microscopic disease or as a salvage treatment for unresectable primary tracheal carcinoma (PTC); however, there is no clear definition of the role of radiation therapy as adjuvant therapy because few factors related to RT planning or dose have been described (Grillo and Mathisen, 1990; Gelder and Hetzel, 1993; Regnard et al., 1996; Gaissert et al., 2009). Indications for adjuvant treatment are: positive margins, vascular invasion advanced tumor stage (T3, T4), extracapsular extension, perineural (PNI) or lymphovascular invasion. In the Netherlands Cancer Registry, patients had median survival of 91, 82, 11 and 3 months, if underwent resection without radiotherapy, resection with radiotherapy, radiotherapy alone or no therapy, respectively (Honings et al., 2007; Wen et al., 2018). Yang et al. evaluated the impact of positive margins on prognosis and adjuvant therapy on overall survival (OS) of patients with tracheal ACC. In the subset of patients with positive margins, there was no significant difference in survival between patients who did or did not receive postoperative radiation therapy (5-year survival: 82 % vs 82.4 %, $p = 0.80$), even after multivariable adjustment (HR, 1.04; 95 % CI: 0.21–5.25; $p = 0.96$) (Jeffrey Yang et al., 2020). Additional investigation is needed to further elucidate the role of adjuvant RT after resection for patients with PTC (Yusuf et al., 2019). In the Chinese National Cancer Center 191 patients with ACC, treated from 1967 to 2017, were selected. The multivariate analysis showed that the complaint duration (<7 months or ≥ 7 months) and treatment methods (R0 resection, R1 resection with RT, R1 resection without RT) were independent prognostic factors for the DFS of R0/R1 resected patients ($P < .050$), while the tumor size (≤ 3 cm or > 3 cm) and treatment methods were independent prognostic factors for the OS (Wang et al., 2019). In a retrospective chart review (Je et al., 2017), 13 and 9 patients received adjuvant (median dose 59.4 Gy) and definitive RT (median dose 74.4 Gy), respectively. The overall response rate for definitive RT was 77.8 % and two-thirds of patients lived for > 5 years after treatment. The 5 and 10-year local progression-free survival (LPFS) rates in the definitive RT group were 66.7 and 26.7 %, respectively. Högerle et al. evaluates a small number of 38 patients presenting with a primary ACC of the trachea, treated by surgery ($n = 20$) and/or radiotherapy with either C12 ($n = 7$) or photons ($n = 24$). The median follow-up for all patients was 74.5 months. In patients who received multi-modal treatment including surgery and adjuvant radiotherapy, the 5-year OS was 84 % (10-year: 84 %). The 5-year freedom from local progression (FFLP) was 100 % (10-year: 100 %), and the 5-year freedom from distant progression (FFDP) was 65 % (10-year: 65 %) (Högerle et al., 2019).

Levy et al. (Levy and Omeiri, 2018) analyze 31 patients with thoracic adenoid cystic carcinoma (74 % tracheal and 26 % bronchial) who received adjuvant ($n = 22$) and definitive radiotherapy ($n = 9$). The mean delivered dose was 62 Gy (40−70 Gy) and eight patients had a radiotherapy boost (mean 19 Gy, range 9−30 Gy, two con endobronchial brachytherapy). With a median follow-up of 5.7 years, the 5 year of OS and PFS rates were 88 % and 61 %, respectively. In the univariate analysis, a dose of radiotherapy ≤ 60 Gy, an age ≥ 50 years and the presence of PNI were associated with decreased PFS. Unresectable tracheal ACC can effectively be treated with definitive, especially high-dose (> 60 Gy), radiotherapy, which yields relatively long-term survival (>5 years) and local control that varies between 20 % and 70 %, (Napieralska et al., 2016). The major pattern of failure is lung metastasis (Maziak et al., 1996), regardless of whether surgery was

performed. After resection with/without RT, some patients have been reported to develop severe complications: recurrent laryngeal nerve palsy, tracheal stenosis, dysphagia, and airway granulation and the RT plan or dose should accordingly be tailored in some patients (Webb et al., 2006; Prommegger and Salzer, 1998; Honings et al., 2010; Lee et al., 2011).

4. Neuroendocrine tumors

Neuroendocrine tumors (NET) include a large variety of cancers with an increasing incidence over the last decades, mainly developed in gastro-entero-pancreatic (~5/100000/year) and bronchopulmonary systems (1–2/100000/year). NET may be part of MEN1 syndrome (Lawrence et al., 2011; Oberg et al., 2012). Despite the paucity of data, RT could be evaluated in this setting, as reported in Tables 1 and 2.

Gastroenteropancreatic neuroendocrine tumors (GEP-NET): Surgical resection with negative margins (R0) is the only potentially curative treatment of localized pancreatic neuroendocrine tumors (PNET). A significant proportion of patients present with unresectable disease, and, especially in pancreatic neuroendocrine carcinoma (NEC), with metastatic disease. PNET has a more favorable prognosis compared to pancreatic adenocarcinoma; so maximizing local control (LC) is very important in this case. A systematic review conducted by Chan et al. reported data from interesting studies (Chan et al., 2018; Saif et al., 2013; Arvold et al., 2012; Contessa et al., 2009; Strosberg et al., 2007); a recent paper published by Iwata et al. (2017) reported outcomes of chemoradiation (RT-CT) for unresectable PNET. The articles show that RT can be a suitable option for post-surgical (positive margins or poor pathologic features) or unresectable/borderline PNET, allowing a good LC, with an acceptable toxicity. Limits of the studies are that they are retrospective and with a limited number of patients; they include different histologies and there is a majority of less aggressive subtypes in patients not treated with RT (Table 1). Only one study in literature (Goyal et al., 2012) reports a case of a nonresectable PNET treated with stereotactic radiotherapy (SBRT) (30 Gy in three fractions), with complete response at 31 months and alive free of disease at the last follow-up (3 years). Despite the difficulty to draw conclusions from a single case, authors concluded that PNET appears to be radiosensitive and has to be considered for SBRT treatment. SBRT is also a valid option for oligometastases, permitting to delay systemic treatments; there are no studies ongoing evaluating the association of RT/SBRT with targeted therapies (everolimus and sunitinib) actually used in the metastatic setting.

In G1 and G2 anorectal NETs, endoscopic resection or anterior rectal resection is indicated, while G3 anorectal NEC are more aggressive tumors. Brieau et al. (2015) shows that in anorectal G3 NECs, RT-CT can obtain a similar outcome of surgery in terms of PFS or OS. Conservative management with RT-CT could avoid a definitive colostomy, with tolerable toxicities. Similar results are reported by Voong et al. (2017), where RT-CT provided LRC for the majority of patient's lifetime (Table 2).

4.1. Bronchopulmonary neuroendocrine tumors (BP-NET)

Small cells lung carcinoma (SCLC) guidelines are well known; but for typical (TC) and atypical carcinoids (AC) therapeutic management is not clearly defined, due to the rarity of these tumors and to the absence of prospective trials; so multidisciplinary evaluation is often necessary in order to assess the best cost-effective therapeutic option. Surgical resection is the treatment of choice in localized TC or AC. In the adjuvant setting, there is a lack of consensus between guidelines. Filosso et al. (2013) reported that survival was influenced by the presence of lymph-node involvement and tumor histology. Locoregional recurrences and distant metastases were more frequent in AC. Carretta et al. (2000) reported five patients with hilar nodal (N1) involvement treated with postoperative mediastinal RT. No locoregional recurrence was observed, but it can be related to the low incidence of recurrence generally observed after a complete resection. Authors concluded that the role of adjuvant treatments in AC is uncertain and should be evaluated in specific trials. In a recent paper of Herde et al. (2018) 6 patients (5 with AC) received postoperative RT-CT (1 RT only) for positive microscopic margins or positive mediastinal nodes, showing optimal outcomes. Then, postoperative RT in bronchial carcinoids may be offered in R1 resections and/or mediastinal lymphadenopathy (N2). Adjuvant RT seems to be of utility mainly in the more aggressive AC. The role of RT in locally advanced and/or unresectable setting appears unclear. Wirth et al. (2004) reviewed cases of patients with bronchial carcinoids treated with CT with or without RT. Three AC patients (stage IIIA or B) underwent RT-CT; two were alive with stable disease, the other had partial response. One patient with TC in stage IIIA was alive with stable disease after CT. Authors argued that advanced or unresectable disease can

Table 1
Characteristics, toxicities and efficacy of the examined studies for PNET.

Author -year	*A Age - range*	*N° pts*	*Treatment*	*Median RT dose/ Technique*	*Acute toxicity (G3or +)*	*Late toxicity (G3or +)*	*Efficacy*
Iwata et al., 2017	50 (37–76)	11	2 RT + CT 9 RT only For unresectable cancers	50–54 Gy (25–30fx) 3DCRT (9) 60 Gy /30fx IMRT (1) Protons: 54 GyE/30fx (1)	G3 diarrhea requiring hospitalisation for hypokalemia (1) Vomiting requiring hospitalization (1)	Gastrointestinal hemorrhage from gastric antral vascular ectasia at 7 months from RT (1)	LC 100 % Median PFS: 5,5 months Median OS: 35,9 months
Saif et al., 2013	52 (38–63)	6	3 RT-CT alone, 3 RT-CT after surgery	50.4 Gy/28–3D-CRT or IMRT	Grade 3 diarrhea (1)	NR	2/3 postoperative recurred with DM at 12 months and 27 months. Locally adv: 1/3 PD on liver at 13 months, then SD with Sandostatin
Arvold et al., 2012	58 (43–74)	16	16 RT +/-CT after surgery with involved margins	50,4 Gy/28 2D-RT (6), 3D-CRT(6), IMRT (4)	Small bowel enteritis G3 (1)	No late toxicities	1/16 (6%) experienced LR, 5/16 (38 %) developed DM 5 years OS: 28%
Contessa et al., 2009	51 (19–77)	14	RT +/- CT (8 unresectable, 6 post surgery with positive margins or N+)	58.4 Gy	1 gastric perforation 1 septic colitis	1 gastrointestinal bleeding 1 duodenal stricture 1 duodenal perforation causing death at 21 months	Median OS: 2,1 years
Strosberg et al., 2007	46 (37–57)	6	RT-CT for unresectable locally advanced	50.4 Gy/28 for 2 patients; unknown for other 4; 3D CRT	Grade 3 neutropenia (1)	NR	LC 100 % All patient alive in the follow-up period (29 months)

Legends Table 1: RT: radiotherapy; CT: chemotherapy; 3D CRT: 3D conformal RT; IMRT: Intensity modulated radiation therapy; 2D RT: 2D radiotherapy; LC: local control; PFS: Progression free survival; SD: stable disease; TTP: time to progression; DM: distant metastases; RR: regional recurrence; OS: overall survival; NR: not reported; LR: local recurrence.

Table 2
Characteristics and efficacy of study analysed for anorectal and lung neuroendocrine carcinoma.

Author -year	*A Age range*	*N° pts*	*Histology*	*Tumor site*	*Treatment*	*Median RT dose*	*Toxicity*	*Outcomes*
Brieau et al., 2015	63 (36–85)	12	NEC (G3)	Anorectal	RT-CT only	Dose tot 58 Gy: range 44–66 (40–50 Gy to pelvic nodes + tumor Boost 10–20 Gy on tumor site in ten patients)	NR	Median PFS: 13,2 months Median OS: 39,2 months LC: 93 % (1 LR, 7 DM, 5 both)
Voong et al., 2017	61,5 (42–74)	10	Pure NEC (8) NEC with minor component of ADC (2)	Anorectal	Postoperative RT-CT (1) Preoperative RT-CT (2) RT-CT only (7)	50,4 Gy (45–60 Gy) 4 IMRT 6 3DCRT	No acute toxicity G3 or G4 Small bowel obstruction 7 weeks after RT, resolved with conservative treatment	LRC: 1 year 70 %, 2 years 56 % PD in 70 % (7 pt → DM in 6) 2 years PFS: 30 % 2 years OS: 46 %
Carretta et al., 2000	56,5 (13–76)	5	TC (4) AC (1)	Lung	Surgery + postoperative RT in N1 patients	56 Gy (range 45–58)	NR	LC 100 % (No locoregional recurrence observed)
Herde et al., 2018	54 (24–83)	6	TC (1) AC (5)	Lung	Surgery + postoperative RT-CT (5) or postoperative RT only (1) for R1 and/or N+	Total RT doses: 50 Gy (3) 41 Gy (1) 44 Gy (1) 1 NR	NR	2 years OS: 93 % 5 years OS: 80 % 10 years OS: 80 %
Wirth 2003	63,5 (33–81)	4	TC (1) AC (3)	Lung	Locally advanced / unresectable tumors: CT + RT-CT	Total RT doses: 54 Gy (2) 46 Gy (1) 1 NR	NR	SD (3) PR (1) Median OS: 20 months
Colaco and Decker, 2015	73,3 (63,7–82,4)	4	TC (2) AC (2)	Lung	SBRT	54 Gy/3fx (2 distant from PBT) 50 Gy/5fx (2 near to PBT)	No severe acute or late toxicities	LC 100 % (no locoregional recurrences) DM in 1 pt with death 2 months after SBRT 1 death at 14 months for ischemic colitis
Singh et al., 2019	66,5 (40–83)	10	TC (9) AC (1)	Lung	SBRT	Median prescription RT dose: 50 Gy (range 40–60 Gy) in 5–10 fx	1 pt had focal fibrosis 1 had symptomatic pneumonitis (G3)	Median OS: 27,1 months (range 5,5–56) (Median OS 20,5 months for BED $\leq$ 95; Median OS 33,7 months for BED $>$ 95)

Legends Table 3: ADC: adenocarcinoma; NEC: Neuroendocrine Carcinoma; LRC: Locoregional control; IMRT: Intensity Modulated Radiation Therapy; 3DCRT: conformal RT; PD: Progression Disease; PFS: Progression free survival; OS: Overall Survival; DM: Distant metastases; NR: Not reported. NR: Not reported; LC: Local control; SD: Stable disease; PR: Partial response; OS: Overall survival.

respond to RT-CT like SCLC, but with lower response rates. SBRT is a good alternative for patients not amenable to surgery, because of the relative radioresistant nature of BP-NET, and it remains a valid option for oligometastatic patients (Colaco and Decker, 2015; Singh et al., 2019). A retrospective large review showed that patients with inoperable early-stage (I-IIA) TC treated with SBRT (doses 50–55 Gy in 4–5 fractions) have a median OS significantly better than patient treated with 3D-CRT (Wegner et al., 2019). SBRT doses can vary from 50–54 Gy in 3–5 fractions (Colaco and Decker, 2015) to 50–60 Gy in 5–10 fractions (Singh et al., 2019), showing better results for BED- $>$ 95 Gy (Singh et al., 2019) (Table 2).

5. Hepatobiliary tumor

Hepatobiliary cancers are considered rare and heterogeneous group of malignancies. The behaviour of these tumors makes loco-regional control of great significance. Nowadays, hepatocellular carcinoma (HCC) is increasing in incidence, due to the aging cohort with chronic hepatitis C infection and the surge of non-alcoholic fatty liver disease and obesity and is the fourth leading cause of cancer-related death (Global Burden of Disease Liver Cancer Collaboration, 2017). Hence the importance of dealing with this topic. Surgical approach remains the gold standard for curative treatment including either a partial hepatectomy or liver transplantation. In patients with unresectable but localized HCC, there is no clear management consensus. Suggested options include transarterial chemoembolization (TACE), transarterial radioembolization (TARE), radiofrequency ablation (RFA), and stereotactic body radiotherapy (SBRT). Currently, there is only few prospective studies comparing the efficacy of the approches above mentioned. There is an increasing number of articles in literature supporting the usefulness of SBRT for patients with unresectable, locally advanced, or recurrent HCC. Sanuki et al. reported the results of a retrospective analysis in 185 Japanese patients, with 70 % of patients alive 3 years after SBRT and 91 % of local control (LC) (Sanuki et al., 2014). Similarly, other studies performed in North America have shown overall survival (OS) rates of 67–75 % one to two years post-SBRT and LC rates ranging from 87 to 100 % (Cárdenes et al., 2010; Andolino et al., 2011; Bujold et al., 2013; Culleton et al., 2014). Kang et al. in a prospective phase II study evaluated 47 patients with primary HCC who had received 1–5 TACE treatments with incomplete response, unsuitable for RFA (Kang et al., 2012). Patients received SBRT in three fractions for a total dose of 42–60 Gy. At two years after SBRT, OS and LC were 68.7 % and 94.6 %, respectively, with a complete response by RECIST criteria of 38.3 %. SBRT may be indicated for all tumors, regardless of their site. Given the excellent response and local control rates in primary and recurrent HCC (Table 3), SBRT is also an interesting approach as a bridge to transplant and potential conversion of inoperable patients (Huang et al., 2012; Guarneri et al., 2016). The bridging therapy induces tumor reduction with a favorable toxicity profile, preventing tumor progression during the waiting period. Despite the absence of randomized data, SBRT is an effective liver-directed therapy for LC with a safe toxicity profile.

Biliary tract tumors are a group of rare neoplasms that in most cases occur in a locally advanced stage. They are often susceptible to surgical intervention but have important recurrence rates after surgery. They consist of cholangiocarcinomas (CCA), which include extrahepatic, peri-

Table 3
Characteristics and efficacy of studies examined for in primary and recurrent HCC.

Author-year	*Trial*	*N° pts*	*Age Median (range)*	*Tumour site*	*Treatment*	*RT dose*	*Toxicity*	*Efficacy*
Sanuki et al., 2014	Retrospective	185	73 (40–89)	HCC	SBRT	35–40 Gy/ 5 fr	G3-G4 events: 13 %	3-year LC: 91 %
Cardenes et al., 2010	Phase I	17	61 (46–83)	HCC	SBRT	36 Gy/3 fr	Classic RILD in 3/ 17 pts	2-yr LC: 100 %
Andolino et al., 2011	Retrospective	60	59 (24–85)	HCC	SBRT	24–48 Gy/3–5 fr	15 % G3 LFT elevation	2-year LC: 90 %
Bujold et al., 2013	Phase I/II	102	69 (40–90)	HCC	SBRT	Median dose 36 Gy/6fr	Classic RILD in 7 pts	1-yr LC: 87 %
Culleton et al., 2014	Retrospective	29	63 (44–82)	HCC	SBRT	Median dose 30 Gy/6fr	G3-G4 events: 0%	1-yr LC: 100 %
Kang et al., 2012	Phase II	47	nd	HCC	SBRT	Median dose 57 Gy/3fr	4.3 % G4 GI perforation	2-year LC: 94.6 %
Huang et al., 2012	Retrospective	36	67 (36–86)	recurrent HCC	SBRT	Median dose 37 Gy/ 4–5fr	Gastric ulcer in 2 pts	1-yr LC: 87.6 %

hilar, intrahepatic and gallbladder tumors. The prognosis for CCA is poor; however, in selected patients it is possible to offer treatments, surgical and non-surgical, with curative purposes. To date, there are no randomized studies available on the role of adjuvant radiotherapy alone or associated with chemotherapy in patients who have undergone surgery. For patients with positive margins or involved regional lymph nodes, data derived from some meta-analyses, retrospective data and a phase II study support the role of adjuvant radiotherapy in both gallbladder carcinoma and extrahepatic CCA (Horgan et al., 2012; De Oliveira et al., 2007; Ben-Josef et al., 2015). However, most patients with CCA present themselves at diagnosis as not amenable to surgery. In this context, the median survival is between 2, 3 and 9 months (Endo et al., 2008). The rarity of this pathology strongly limits the possibility of collecting data for a better definition of the management of unresectable diseases; most of the evidence is derived from retrospective studies that include heterogeneous cases of tumors. In a retrospective study, 84 patients with unresectable intrahepatic cholangiocarcinoma were examined to evaluate the effectiveness of radiation therapy. Thirty-five out of 84 (41.7 %) patients received radiation therapy. This study showed an improvement in both OS and LC associated with radiation treatment with or without TACE compared to TACE alone or supportive care. The disease control rate with radiotherapy was 85.7 %. There was a significant improvement in median OS with radiation therapy (9.5 months versus 5.1 months, $p = 0.0003$). For patients with central tumors, radiation therapy was particularly beneficial with a median OS of 13.3 months compared to 3.5 months without radiation therapy (Chen et al., 2010). Radiation therapy with EBRT or SBRT may be used for patients with unresectable biliary tract tumors. The evidence supports the consideration of radiotherapy for treatment of unresectable intrahepatic CCA. However, prospective randomized trials are needed to define the optimal combination of therapies.

6. Soft tissue sarcoma and desmoid tumor

Soft Tissue Sarcomas (STSs) are a rare disease accounting less than 1% of all adult neoplasms (Ray-Coquard et al., 2012). Surgical excision is the cornerstone of localized STSs (Fletcher et al., 2002). Perioperative treatments are often indicated, but if the role of radiotherapy is well recognized in case of conservative surgery, the role of chemotherapy in localized disease is still controversial due to the conflicting data on efficacy and treatment related toxicity (Hatcher et al., 2017). Postoperative RT is delivered after conservative surgery in localized advanced soft tissue sarcoma. Yang et al. (1998) randomized 141 high- and low-grade soft tissue sarcoma patients to receive or not external beam radiotherapy (EBRT) after wide excision. Local recurrence rate was 0% in EBRT group compared to 22 % in surgery alone group ($p = 0.001$), EBRT benefit was confirmed also in the low-grade STS patients ($p = 0.003$). Similar results were obtained by Pisters et al. (1996) in a brachytherapy series. In historical series postoperative radiotherapy correlated with edema, fibrosis, joint stiffness and bone fractures; preoperative RT, due to the smaller radiotherapy volume and lower doses compared to postoperative RT (50 Gy vs 60–66 Gy), is associated with low risk of late toxicity compared to postoperative RT even if it is associated to high risk of wound complications (O'Sullivan et al., 2002). The better timing of radiotherapy is still not well defined and nowadays it is a clinicians' choice. The introduction of new technologies such as intensity modulated radiotherapy (IMRT) showed optimal results in terms of local control and significant reduction of toxicities both in neoadjuvant and adjuvant setting (Alektiar et al., 2008; O'Sullivan et al., 2013). In particular, IMRT is recommended in neoadjuvant setting in critical location such as retroperitoneum to reduce doses to organs at risk such as bowel and kidneys (Shah et al., 2016). A growing role of radiotherapy in STSs is in oligometastatic disease in particular SBRT is becoming a valid alternative to surgery in patients with limited number of metastasis (Loi et al., 2018; Baumann et al., 2016; Navarria et al., 2015).

Moreover, an important role in the treatment of sarcomas is played by intraoperative radiotherapy (IORT) used as an alternative boost technique in patients at high risk of local recurrence. The IORT technique allows the administration of a high dose of radiation in a single fraction on the tumor bed during surgery, producing much smaller irradiated volumes than EBRT, which could provide a dose escalation approach without an increase in functional deficits and important late side effects (Roeder, 2020). Recently, ESTRO IORT Task Force published ACROP recommendations regarding the application of IORT in the treatment of sarcomas providing a detailed description of the technique (Roeder et al., 2020).

Desmoid tumor (DT) or aggressive fibromatosis is a rare clonal fibroblastic characterized in 85 %–90 % of cases by the mutations in the b-catenin gene (Penel, 2017). The incidence is of 1–5 cases per million of the population per annum (Penel et al., 2016). Historically, DT considered as a soft tissue sarcoma, has been treated with surgery with a local control of about 80 %. The observation of spontaneous regressions in about 20 %–30 % of case and a progression free survival rate of 50 % at five years in case of untreated disease justified a "watchful waiting" strategy (Briand et al., 2014; Colombo et al., 2015). Nowadays, surgery is reserved to progressed disease during follow up or in case of symptomatic disease at diagnosis (Salas et al., 2011). In DT radiotherapy is indicated in inoperable symptomatic disease or in case of progressive disease after surgery (Santti et al., 2017). RT administered for a total dose of 56 Gy (2 Gy daily) provides optimal control rate with acceptable toxicity profile (Keus et al., 2013). In DT overall local control after radiotherapy is 75–95 %. Adjuvant radiotherapy may reduce the risk of local relapse in case of inadequate surgery, in a recent systematic review, including 28 studies analysing treatment options in DT, three of the included studies reported a statistically significant higher local control rate in patients treated with surgery and radiotherapy compared to surgery alone (Yao et al., 2014). The management of desmoid tumors needs a careful evaluation of the risk of local recurrence and the morbidity of active treatment such as surgery and/or radiotherapy.

7. Ovarian cancer

Epithelial ovarian cancer comprises one-fourth of all gynaecological malignancies, accounting for most of the cancer-related deaths in this setting (Fujiwara et al., 2002). Most of the patients present with advanced disease. The standard treatment included combination therapy, with cytoreductive surgery and adjuvant chemotherapy based on taxane and platinum compounds. In up to 70 % of cases with advanced ovarian cancer, recurrence is observed during disease course, predominantly with the occurrence of peritoneal carcinomatosis or distant dissemination. However, a not negligible percentage of patients develop isolated loco-regional recurrence (Yahara et al., 2013). The role of radiation therapy in this clinical setting has changed during the years. Historically, whole-abdominopelvic irradiation has been used as consolidation therapy after primary treatment in high-risk patients, with the intent to eradicate residual subclinical disease (MacGibbon et al., 1999). Treatment volumes usually included the whole peritoneal cavity with a common prescribed dose of 30 Gy in 1.2–1.5 daily fractions and a subsequent 15−20 Gy to pelvic and para-aortic nodes (Chundry et al., 2016). Due to the unsatisfactory clinical results and the poor compliance to therapy together with the availability of highly effective chemotherapy regimens, whole abdominal irradiation is no longer employed in routine clinical practice. Interestingly, selective strategies including volume-directed involved-field radiotherapy were employed for limited recurrent disease, with no metastatic spread (Kunos et al., 2012; Brown et al., 2013; Albuquerque et al., 2016; De Felice et al., 2017). As an example, in the series by Brown et al. (2013), patients were treated mostly with conventional fractionation delivering a median dose of 59.2 Gy (range: 45–68.2 Gy), targeting localised nodal or extranodal disease relapse. No major toxicities were observed. In-field control at 5-years was 71 %, while progression-free survival (PFS) and overall survival (OS) were 24 % and 40 %, respectively. Clear-cell carcinoma had a better PFS (75 % vs 20 %) and OS (88 % vs 37 %) compared to other histological types. Smaller tumors were easier to control locally. Similar positive results were observed in the series by Albuquerque et al. (2016), in which 10-year disease-free survival (DFS), OS and local-recurrence free survival rates were 20 %, 19 % and 60 %, respectively. Another clinical setting in which radiotherapy was used is oligometastatic disease, a transitional condition made up of 1–5 detectable metastases, with an intermediate prognosis between localised and widely disseminated disease, in which local control may trigger improved survival (Ricardi et al., 2013). Stereotactic ablative radiotherapy (SABR) delivers, with an ablative purpose, a high dose per fraction with abrupt dose fall-off. It is particularly suitable as local treatment in oligometastatic disease (Franco et al., 2014). Lazzari et al., reported on a series of patients affected with oligorecurrent or oligoprogressive ovarian cancer treated with SABR delivering a median dose of 24 Gy in 3 fractions (82 patients/156 lesions). The complete response rate was 60 %, while the objective response rate (including complete and partial responses and stable disease) up to 93 %. No major adverse events were reported. Median time to the beginning of a new systemic treatment was 7.4 months and a third of the patients were free of disease at 1 year. Actuarial local PFS and OS were 68 % and 71 %, respectively, with most of relapses observed outside the radiotherapy field (Lazzari et al., 2018). The chance to observe a complete response was demonstrated to be higher for patients aged ≤60 years treated on planning target volumes ≤18 cm^3, preferably on lymph node disease, with a biologically effective dose >70 Gy (Macchia et al., 2020). In general, RT, especially delivered with modern techniques, represent a reliable and effective treatment option with a mild toxicity profile for ovarian cancer patients, particularly for (oligo)recurrent-progressive disease (Table 4) (Iorio et al., 2019).

8. Endocrine tumor

*Adrenocortical carcinoma (*AcC*)* is a rare and lethal endocrine malignancy which has an incidence of 1–2 cases per million people per year; AcC has a high risk of recurrence (5-year disease-free survival range from 13 % to 82 %) and a poor prognosis (5-year OS ranged from 10 to 46 %) (Bilimoria et al., 2008). Despite radical surgery is still the only curative therapy, rates of local control after apparently total resections range from 19 % to 60 % (Milgrom and Goodman, 2012a). These findings suggest additional approaches are needed to control and delay tumor progression. Traditionally, AcC has been considered as radio-resistent malignancy based on previous case series. Recently, adjuvant RT has demonstrated benefits through reducing recurrence risk. A recent systematic review and meta-analysis published by Viani and Viana (2019), assessed 48 patients in 8 case series and 136 patients in 4 cohort studies and concluded that RT provides an absolute risk reduction of local recurrence of 28 % in 5 years and the adjuvant treatment remains effective in reducing the locale failure also with negative margins. Despite this significant benefit in terms of local recurrence-free survival (LRFS), relapse free survival (RFS) and overall survival (OS) are not different. Srougi et al. (2017) confirmed the same results and concluded that the impact of RT on RFS and OS is limited by small sample sizes available and because RT do not reduce the risk of distant metastases. The study published by Nelson et al. (2018) evaluated all patients with non-metastatic AcC identified in the 2004–2013 National Cancer Database, comparing the outcome of surgery alone in 1013 pts and surgery with adjuvant RT in 171 pts (14.4 %). Adjuvant RT was associated with a 40 % decreased yearly risk of death (hazard ratio 0.60, 95 % CI 0.40−0.92; p = 0.02) in patients with positive margins and it is the first study to demonstrate a significant survival advantage in selected groups of patients with AcC. Instead, CT was ineffective on survival on multivariariable analysis and these results demonstrate to a greater extent the importance of obtaining early and comprehensive locoregional control for overall outcome and to prevent tumor recurrences in the tumor bed or retroperitoneum, since in these areas the access would be difficult during reoperative surgery due to scar tissue. The retrospective study by Else et al. (2014) evaluated the role of mitotate and RT as adjuvant treatment strategy for AcC 264 patients were available for the evaluation of mitotane therapy (40 % with

Table 4
Characteristics, toxicities and efficacy of the examined studies for (oligo)recurrent-progressive ovarian cancer.

Author-year	*Trial*	*N° pts*	*Age Median (range)*	*Tumour site*	*Treatment*	*RT dose*	*Toxicity*	*Efficacy*
Brown et al., 2013	Retrospective	102	58 (30−81)	Nodal or extranodal	Involved field RT	> 45 Gy	G3-G4 events: 0%	5-year LC: 71 %
Albuquerque et al., 2016	Retrospective	27	59 (29−85)	Nodal, pelvic	Involved field RT	Median dose: 50 Gy	>G3 late effects: 7.5 %	5-year LRFS:70 %
Chundry et al., 2016	Retrospective	33	62 (41−84)	Nodal or extranodal	Involved field RT	50.4 Gy	ND	2-year LC: 82 %
Kunos et al., 2012	Phase II	50	66 (27−82)	Nodal or metastatic	SABR	Median dose: 24 Gy/3fr	Fatigue G2: 16 %	Median OS: 20.2 months Median DFS: 7.8 months
Lazzari et al., 2018	Retrospective	82	60 (37−84)	Nodal or metastatic	SABR	24−30 Gy/3 fr	G3-G4 events: 0%	Systemic-treatment free interval 7.4 months. 1 year-DFS: 33 %

mitotane and 60 % without) and 276 patients for the evaluation of RT (21 % with RT and 79 % without); a total of 42 patients received both adjuvant therapies. RT confirmed the effect on local control within the tumor bed (9% vs 48 % of patients without RT). Mitotane therapy but not RT significantly improved RFS in the multivariate analysis (HR 0.7). What seems interesting is that, when both adjuvant therapies were combined, there was a meaningful additional benefit in term of RFS (HR: 0.4); statistics also show an interaction also for overall survival, although with no statistically significant results. With regards only to patients with R0 resection, considered the most suitable for true adjuvant therapy, only the combination of RT and mitotane increased RFS (HR: 0.2), without increasing the rate of adverse events (Sabolch et al., 2015). Due to the substantial rate of inter-aortocaval nodal metastases up to 25−30% present in historical series, it is current practice to cover the nodal to 45 Gy at 1.8−2 Gy per fraction with a simultaneous integrated boost, whereas the primary post-operative bed receives 50 Gy after an R0 resection or 55–60 Gy after R1 or R2 resection. In conclusion, RT is intended for patients with a high risk for local recurrence (surgical margins R1 or Rx, high grade, tumor size larger than 10 cm or tumor capsule rupture). The only caution regarding adjuvant RT is that it should be avoided in a relevant amount of patients, especially children and adolescents with a TP53 mutation.

The adrenal gland is also a common site for the metastatic spread of many types of solid malignant neoplasm, and data show that the 38 % of patients with cancer are diagnosed adrenal metastases post-mortem.

SBRT provides localised therapy option where surgery is not considered feasible or is used as a non-invasive useful alternative treatment for adrenal primitive or metastatic tumors. In fact, recent evidences show how the risk of complications after adrenalectomy can reach up to 23 % (Desai et al., 2015). SBRT is not associated with catecholamine increases and is capable to maintain adrenal function in some cases of bilaterally treated adrenal tumors. Due to the rarity of primitive AcC, these patients were evaluated together with the metastatic tumors without different reported outcomes (Toesca et al., 2018). Preliminary experiences with SBRT have shown low toxicity rates with grade 2 toxicity from 0% to 15 % and local disease control that ranges between 55%–100% at 1 year. Different fractionations were used in literature; 36 Gy in 3 fractions and 45 Gy in 5 fractions are the most common and report local control rate up to 90–100 % at 2 years. Many studies have shown that BEDs $>$ 100 Gy are needed to obtain optimal local control although most doses used lead to good palliation of symptoms (Milgrom and Goodman, 2012b).

Pineal region tumors (PRTs) represent less than 1% of all primary central nervous system (CNS) tumors. Pineal parenchymal tumors (PPTs), deriving from pinealocytes, are the second largest subgroup of PRTs after germ cell tumors (GCTs) and represent about 10–30 %. According to the WHO classification, PPTs are categorized into well-differentiated pineocytomas (PC), PPTs with intermediate differentiation (PPTID) which represent WHO grade II or III tumors and poorly differentiated pineoblastomas (PB) that are classified as supratentorial primitive neuroectodermal tumors (PNETs). In 2007, papillary tumor of the pineal region (PTPR) was included by WHO as a distinct clinicopathological entity (Stoiber et al., 2010). PCs are the most favorable prognosis: 5-year OS rates have been reported to range from 64 to 91 %. Gross total resection (GTR) is generally curative in PC and adjuvant RT has been showed no benefit in terms of PFS and OS, even after subtotal tumor resection (Clark et al., 2010). Radiosurgery (SRS) alone or in combination with open microsurgery, has been used as a substitute for microsurgical complete removal of PPTs. Balossier et al. (2021) lately analyzed the results following SRS and found 13 studies reporting 175 patients with 15 distinct histological diagnoses, treated by Gamma-Knife radiosurgery (12−20 Gy). As it is reported, for PC SRS could be used as an alternative to surgery and it is sufficient as a primary therapy, with 20-year local control rate of 81 % and survival rate of 76 %.

PBs, considering the risk of metastasizing throughout the craniospinal fluid spaces and neuro-axis, have a poor prognosis (5-year OS 10 %). Findings show that combined therapies which include GTR, curative or prophylactic craniospinal irradiation (CSI) followed by a boost to the primary tumor with doses $\geq$ 54 Gy and multi-agent chemotherapy (CT) correlate with enhanced results. 2-year survival rate of 60 % has been showed in patients received surgery plus RT plus CT (Kumar et al., 2018; Chintagumpala et al., 2009). Regarding SRS for PBs, Iorio-Morin et al. reported an actuarial 5-year local control and survival of 27 % and 48 %, respectively. Although these results were superior to previous experiences, PBs have to be aggressively treated with immediate surgery. SRS alone seems ineffective in treating but it seems to have the potential to control local tumor growth in adjuvant setting, in the context of multimodality strategy or as salvage therapy for locally recurrent tumors (Iorio-Morin et al., 2017).

PPTIDs constitute approximately 10 % of all PPTs. The 5-year OS has been estimated at 74 % for grade II and 39 % for grade III. Mallick et al. (2016) published in 2016 a review evaluating 127 patients with PPTID. Use of adjuvant RT with doses of 50.4−54 Gy seems to be associated with better OS (median OS, 252 vs 168 months; $p = 0.009$). The authors concluded that patients diagnosed with leptomeningeal spread have to be treated with CSI. But considering that the leptomeningeal recurrence rate is only 11.8 % (15/127), it is not recommended for all the patients to undergo prophylactic CSI.

Regarding data on SRS for PPTID patients, they are controversial due to the rarity and heterogeneity of these tumors. However, the authors suggest using SRS for grade II and grade III PPTIDs as for PCs and PBs, respectively (Stoiber et al., 2010; Clark et al., 2010; Balossier et al., 2021; Kumar et al., 2018; Chintagumpala et al., 2009; Iorio-Morin et al., 2017).

PTPRs originate from specialized ependymocytes of the subcommissural organ. The largest retrospective multicenter series of 44 patients reported the results of combined therapeutic approach (surgery plus adjuvant RT and CT), showing a high rate of local recurrence: PFS at 48 and 72 months were 37 % and 26,6% respectively (Fauchon et al., 2013). With reference to SRS, Iorio-Morin et al. (Kumar et al. (2018)) confirmed these results and found a poor actuarial local control (33 % at 5 years) with excellent survival (100 % at 5 years). Interestingly, these data suggest that biopsy plus SRS seem to have the same outcome as GTR with regards to survival (Iorio-Morin et al., 2017). Moreover, in case of recurrence, repeat SRS as exclusive treatment or after debulking microsurgical resection might be a valid alternative as the success rate is expected to reach the 80 % (Iorio-Morin et al., 2017).

9. Conclusions

Roundly a quarter of all diagnosed cancers are descripted as Rare tumors, and this incidence should be incremented in the future. Due to the limit of rareness, the proper treatment approach is not well defined. Surely, as highlighted by the present analysis, the radiotherapy option is not a rare indication in this setting and the role of Radiation Oncologist must not be neglected. Considering the technological advances and the results obtained from the administration of high doses of radiation in small volumes, stereotaxic radiotherapy treatment could be a valid alternative to surgery. A multidisciplinary approach is necessary to offer the best practice in treating rare cancers.

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