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Controversies in Radiation Oncology

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Controversies in Radiation Oncology

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Breast Cancer

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Abstract

Radiation therapy plays an integral role in the multidisciplinary management of breast cancer. In appropriately selected patients, radiotherapy not only prevents local recurrences by eliminating residual disease but also results in improved survival. However, not all patients have the same risk of harboring residual locoregional disease, resulting in considerable controversy regarding the role of radiotherapy in individual scenarios. Evidence from clinical trials and observational data analyses can help identify which patients with breast cancer are most likely to achieve a net benefit from adjuvant radiation therapy, both after lumpectomy and mastectomy. Additionally, evidence is emerging now about novel approaches in breast radiotherapy that may reduce burden or toxicity in ways that can optimize the therapeutic ratio, including hypofractionated whole breast radiation, accelerated partial breast irradiation (APBI), intensity-modulated radiation (IMRT), and cardiac avoidance techniques. The objective of this chapter is to review both established and emerging evidence regarding these important issues in an effort to clarify the rationale for increasingly complex and individualized decisions regarding breast radiotherapy.

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1 Introduction

Radiation therapy plays an integral role in the multidisciplinary management of breast cancer. In appropriately selected patients, radiotherapy substantially decreases the risk of recurrence and results in improved survival. Within the previous two decades, considerable progress has been made toward selecting patients most likely to benefit from radiation, along with technical improvements that minimize the burden and toxicity associated with treatment while maximizing clinical benefit.

In an effort to clarify the rationale for increasingly complex clinical decisions, this chapter reviews the rich literature from practice-changing clinical trials in recent years, with an emphasis on the indications for radiation in the context of evolving surgical and systemic treatments, optimal approaches that maximize the therapeutic ratio, and appropriate treatment targets, both after breast-conserving surgery and mastectomy.

2 Early-Stage Disease and Breast Conservation

2.1 Radiation After Breast-Conserving Surgery

Several randomized trials have demonstrated equivalent survival after mastectomy as compared to breast-conserving surgery with radiation in appropriately selected patients, allowing women to choose a more limited surgical procedure without compromising disease control (Fisher et al. 2002a; Arriagada et al. 1996; Veronesi et al. 2002; Poggi et al. 2003; van Dongen et al. 2000; Blichert-Toft et al. 1992). Radiation therapy has long been recognized as a key component of breast-conserving therapy, with results from numerous randomized trials demonstrating that postoperative radiation substantially reduces the risk of locoregional recurrence (Fisher et al. 2002a; Clark et al. 1996; Ford et al. 2006; Liljegren et al. 1999a; Veronesi et al. 2001a). For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 randomized trial, the 20-year ipsilateral breast tumor recurrence rate was 14.3 % after lumpectomy and whole breast radiation versus 39.2 % after lumpectomy alone (Fisher et al. 2002a). Adjuvant radiotherapy after breast-conserving surgery has been recommended in consensus guidelines for over two decades (NCCN 2014) and is included as a measure of treatment quality (Surgeons ACo Commission on Cancer Quality of Care Measures; National Quality Measures for Breast Centers).

More recently, the improvement in locoregional control with radiotherapy has been associated with reduction in the overall risk of a recurrence and modest survival benefit as well. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of data from 10,801 individual patients in 17 studies demonstrated that radiation reduced the 10-year risk of any recurrence from 35 to 19.3 % and reduced the 15-year risk of death from breast cancer from 25.2 to 21.4 % (Clarke et al. 2005; Darby et al. 2011a). Similar findings were observed in a pooled analysis that demonstrated a three-fold increase in ipsilateral breast tumor recurrence and an 8.6 % increase in mortality with omission of radiation after breast-conserving therapy (Vinh-Hung and Verschraegen 2004).

However, while the relative benefits of radiation are similar for all patients, the absolute benefit obtained from radiotherapy varies considerably according to patients' baseline risk. The EBCTCG analyses have suggested that the survival benefit may be limited to those who obtain the largest absolute risk reduction from treatment, rather than those in whom the absolute benefit in recurrence risk reduction is less than 10 % (Darby et al. 2011a).

2.2 Omission of Radiation After Breast-Conserving Surgery in Patients with Favorable Features

The prevalence of early-stage breast cancer in a mammography-screened population raises concerns about potential harm associated with

overtreatment. With population-based screening, the incidence of in situ and early-stage invasive disease with favorable prognoses has nearly tripled, while the incidence of later-stage invasive disease has only slightly decreased (Glass et al. 2007; Jemal et al. 2007). Some have suggested that this increase in the incidence of early-stage breast cancer without a corresponding decrease in the incidence of advanced stage breast cancer is reflective of substantial overdiagnosis, accounting for approximately one-third of all newly diagnosed breast cancers (Bleyer and Welch 2012), and that screening is having only a modest effect on the rate of death from breast cancer (Welch and Frankel 2011). Furthermore, the risk of distant metastasis is lower for cancers detected by mammography than for tumors detected outside of screening (Joensuu et al. 2004). Given that approximately one-third of all new breast cancer diagnoses occur in women age 70 or older, and considering that the majority of these cases represent early-stage disease (Jemal et al. 2007), decisions surrounding use of adjuvant radiotherapy in this group affect tens of thousands of women.

In light of these epidemiologic trends, it is plausible that a substantial proportion of women in a mammography-screened population have been diagnosed with early-stage breast cancer that would be an unlikely cause of breast cancer-related mortality. In the EBCTCG meta-analysis, it is worth noting that although radiation significantly decreased the incidence of local recurrence, with lumpectomy alone, 69 % of node-negative patients would not have experienced any recurrence (Darby et al. 2011a). This suggests that a large proportion of women might not benefit from adjuvant radiotherapy. Taken together with concern for the burden, morbidity, and cost of adjuvant radiotherapy, researchers have sought to identify a subgroup of breast cancer patients in whom the risk of recurrence after lumpectomy is sufficiently small that consideration may reasonably be given to omission of radiotherapy.

An observational study from Nemoto et al. (Nemoto et al. 1991) published in 1990 noted that after median follow-up of 4 years, in women who underwent lumpectomy alone, no recurrences occurred in tumors <1 cm, and only 1 of 31 patients older than age 70 experienced a recurrence. Since that early observation, numerous prospective trials have unsuccessfully sought to identify a subgroup of patients who could undergo breast-conserving surgery without radiotherapy (Lim et al. 2006; Holli et al. 2009; Fisher et al. 2002b; Winzer et al. 2010; Forrest et al. 1996; Potter et al. 2007; Fyles et al. 2004).

A prospective single-arm study of lumpectomy alone from Harvard (Lim et al. 2006) observed an unacceptably high local recurrence rate of 23 % at 7 years in a highly selected group of patients with presumed low-risk clinical and pathologic features, such as tumor ≤2 cm, margins ≥1 cm, no involved nodes on axillary lymph node dissection, and no lymphovascular invasion or extensive intraductal component. Forty percent of tumors were positive for the estrogen receptor (ER); 49 % were unknown. Similar results were observed in a trial from Finland (Holli et al. 2009), which observed a recurrence rate of 27 % at 12 years with no adjuvant therapy in highly selected patients with the most favorable features suggestive of low aggressiveness, including progesterone receptor positive, well to moderately well differentiated, and low proliferation rate. Thus, even in women diagnosed with breast cancer with presumably low aggressiveness based on clinical and pathologic features, the rate of recurrence after lumpectomy with wide margins appears unacceptably high (16 to 34 %, see Table 1) without postoperative radiation, at least in the absence of systemic therapy.

Because use of tamoxifen is associated with significantly improved locoregional control (Fisher et al. 1989; Early Breast Cancer Trialists' Collaborative Group 1998), investigators hypothesized that in a favorable group of estrogen receptor-positive tumors treated with breast-conserving surgery, tamoxifen might be as effective as postoperative radiation in reducing the rate of ipsilateral breast tumor recurrence. With the objective of determining whether tamoxifen might be used in lieu of radiation, the NSABP conducted the B-21 randomized trial (Fisher et al. 2002b), in which 1009 women were randomized to tamoxifen, radiation, or both. Patients

Table 1 Prospective clinical trials evaluating omission of radiation after breast-conserving surgery in patients with favorable features

Study	*N*	Age	Tumor size	Estrogen receptor positive	Median follow-up	Other eligibility criteria	Adjuvant therapy after breast-conserving surgery	Locoregional recurrence	Statistical significance
Harvard Lim et al. (2006)	81	Median 66 years (range 27–84)	≤2 cm	40 % (49 % unknown)	7.2 years	Margin ≥1 cm, node negative on ALND	No adjuvant therapy	23 %	NA
Finland Holli et al. (2009)	264	>40	≤2 cm	100 % PR positive	12.1 years	Grade 1 or 2 tumors, low proliferation rate, margin ≥1 cm, node negative on ALND	No adjuvant therapy RT	27.2 % 11.6 %	$p = 0.0013$
NSABP B-21 Fisher et al. (2002b)	1009	20 % <50 years	<1 cm	56.7 %	8 years	Negative margins (no tumor on ink), node negative on ALND	Tamoxifen RT + placebo RT + tamoxifen	16.5 % 9.3 % 2.8 %	$p < 0.001$
Germany Winzer et al. (2010)	347	45–75	≤2 cm	93.7 %	9.9 years	Grade 1–2	No adjuvant therapy Tamoxifen RT RT + tamoxifen	34.2 % 9.7 % 13.2 % 6.8 %	$p < 0.001$
BASO II Blamey et al. (2013)	1135	<70	<2 cm	Not reported (estimated at 90 %)	10.1 years	Grade 1 or favorable histology (tubular, mucinous, papillary, or cribiform), negative margins, pathologically node negative	No adjuvant therapy Tamoxifen RT RT + tamoxifen	15.7 % 7.5 % 6.5 % 0 %	$p < 0.001$
Scottish Forrest et al. (1996)	585	<70	≤4 cm	58.6 %	5.7 years	Preferred negative margins, pathologic nodal assessment (23 % were node positive). Received systemic therapy based on receptor status: ER+ received tamoxifen; ER- received CMF	Systemic therapy alone RT + systemic therapy	24.5 % 5.8 %	SS

Italy Tinterri et al. (2014)	749	55–75	<2.5 cm	92.4 %	9 years	Unifocal, no EIC or LVSI, negative margins, 0–3 positive axillary lymph nodes (15 % were node positive)	Endocrine therapy RT + endocrine therapy	4.4 % 3.4 %	NS
Austria Potter et al. (2007)	869	≥50	<3 cm	99 %	4.5 years	Postmenopausal, grade 1 or 2, pathologically negative lymph nodes	Tamoxifen/anastrazole RT + tam/anastrazole	5.1 % 0.4 % ($p < 0.001$) (5 year)	$p < 0.001$
Canada Fyles et al. (2004)	769	≥50	≤5 cm	80.7 %	5.6 years	Negative margins (no tumor on ink), pathologically negative nodes (unless older than 65)	Tamoxifen RT + tamoxifen	17.6 % 3.5 %	$p < 0.001$
CALGB 9343 Hughes et al. (2004, 2013)	636	70	≤2 cm	97 %	12.6 years	Negative margins (no tumor on ink), clinically node negative	Tamoxifen RT + tamoxifen	10 % 2 %	$p < 0.001$

Abbreviations: BCS breast-conserving surgery, *ER* estrogen receptor, *NS* not statistically significant, *PR* progesterone receptor, *RT* radiotherapy, *SS* statistically significant

[a]In the studies presented in this table, there were no significant differences reported in distant metastasis, breast cancer-specific survival, or overall survival

underwent lumpectomy with negative margins (defined as no tumor on ink) and had invasive breast cancer <1 cm with pathologically negative lymph nodes upon axillary lymph node dissection. Estrogen receptor was positive in 57 % of cases, and 20 % of patients were younger than age 50. The incidence of ipsilateral breast tumor recurrence at 8 years was 17 % with tamoxifen, 9 % with radiation, and 3 % with both, leading the authors to conclude that tamoxifen is less effective than radiation in preventing an ipsilateral breast tumor recurrence and that adjuvant radiotherapy is necessary even when tamoxifen is used. An Austrian trial (Potter et al. 2007) of adjuvant endocrine therapy with or without radiation demonstrated a comparatively lower local recurrence rate of 0.4 % and 5.1 % at 5 years, respectively. In the absence of radiation, the local recurrence rate increased to 9 % after 6 years, leading the authors to conclude that further research and longer follow-up were needed to identify more favorable subgroups for whom radiotherapy was not beneficial.

In a German trial (Winzer et al. 2010), patients with estrogen receptor-positive tumors ≤2 cm were randomized to radiation or tamoxifen in a 2 × 2 factorial design. With breast-conserving surgery alone, there was a large excess of local recurrences, but similar event-free survival was observed with endocrine therapy, radiation, or both. However, the limited sample size and corresponding low power limited the impact of this finding. A Canadian multicenter study (Fyles et al. 2004) that included patients >50 years with tumors up to 5 cm found similarly high rates of local recurrence with tamoxifen alone, at 18 % after 8 years, in comparison to 4 % with both radiation and tamoxifen. These disappointing results were tempered by the finding that in tumors less than 1 cm, the 5-year recurrence rate was 2.6 %, and when further limited to patients who were older than age 60, there was no significant difference in local relapse with tamoxifen alone compared to radiation and tamoxifen (1.2 % vs 0 %, respectively, $p = 0.16$). While acknowledging the limitations of a small, unplanned subgroup analysis with limited follow-up, the authors suggest that further studies considering omission of breast irradiation may be best pursued in older patients with small tumors.

In the seminal CALGB 9343 study (Hughes et al. 2004, 2013), enrollment was limited to a favorable group of 636 elderly patients with early, estrogen receptor-positive tumors. Women ≥70 who were clinically node negative and had tumors ≤2 cm that had been resected with negative margins (no tumor on ink) were randomized to treatment with tamoxifen alone or tamoxifen plus radiation therapy. After 10 years, 90 % of patients receiving tamoxifen compared with 98 % of those receiving both radiation and tamoxifen were free from local and regional recurrence. Although the incidence of local recurrence was significantly higher with omission of radiation ($p < 0.001$), there were no significant differences in time to mastectomy, time to distant metastasis, breast cancer-specific survival, or overall survival between the two groups. The absence of a survival benefit in this cohort appears consistent with the observation from the EBCTCG that the survival benefit with adjuvant radiation is not apparent in patients with absolute recurrence risk reduction less than 10 % (Darby et al. 2011a). This study has been widely interpreted as establishing omission of radiotherapy as a reasonable option for similar women who intend to receive endocrine therapy, and the authors advocate that this cohort should have the option of breast-conserving therapy even without radiation.

Even more recently, mature results have emerged from studies in patients younger than those in CALGB 9343. These results include a British trial (Blamey et al. 2013) with a 2 × 2 factorial design that enrolled 1135 patients younger than age 70 with either grade 1 tumors or favorable histology (tubular, mucinous, papillary, or cribriform) measuring <2 cm. Consistent with results from the previous trials of favorable risk patients, the rate of recurrence without adjuvant treatment was unacceptably high at 16 % after 10 years. With either tamoxifen or radiation, the risk of local recurrence was reduced to 7.5 and 6.5 %. However, the greatest benefit was seen in those women who received both radiation and tamoxifen, as these 98 patients experienced no local recurrences. These results led the authors to

suggest that both radiation and tamoxifen may be a reasonable option for women wishing to minimize their risk of recurrence, but that the use of tamoxifen alone may be acceptable for select patients with low-risk tumors who wish to avoid radiation. Similar findings were reported in an Italian study that randomized 749 women age 55 to 75 to adjuvant radiation and endocrine therapy, or endocrine therapy alone. After 9 years, there was no appreciable difference in rates of ipsilateral breast recurrence (Tinterri et al. 2014).

Still, questions remain regarding whether these studies are generalizable to patients with other risk factors, such as close margins, lymphovascular invasion, or high-grade disease. There is also concern that patients in the general population may be less compliant with endocrine therapy than those enrolled on clinical trials. Some have expressed concern regarding omission of radiation in patients who have a longer life expectancy in the absence of longer-term and larger studies. In a population-based analysis of women between age 70 and 79, there was a significant increase in the risk of subsequent mastectomy with omission of radiation (3.2 % vs 6.3 %, $p < 0.001$), (Albert et al. 2012) in contrast to the non-significant difference observed in CALGB 9343. This was especially pronounced in healthy women between age 70 and 74, who had a number needed to treat of 21 to avoid one mastectomy or second ipsilateral breast cancer (Smith et al. 2006). In contrast, in the subgroup of women between age 75 and 79 who underwent pathologic nodal assessment and did not have high-grade tumors, there was no apparent benefit from radiation (Albert et al. 2012).

While the standard of care remains adjuvant radiation following breast-conserving surgery, there is now a consensus (NCCN 2014) that omission of radiation may be a reasonable alternative for highly selected women older than age 70 with small, estrogen receptor-positive tumors. For other patients, the limited and conflicting data on long-term control with endocrine therapy alone remains insufficient to convince most practitioners to consider omitting radiotherapy. The number of trials to date that have unsuccessfully sought to identify a subgroup of patients at low risk of recurrence with endocrine therapy alone after breast-conserving surgery indicates that clinical and pathologic features are inadequate discriminants for precisely indicating which patients are likely to experience treatment failure and, thus, to require therapy. Future efforts are focused on selecting patients at low risk of recurrence based on tumor biology, such as using the 21-gene recurrence score (Mamounas et al. 2010) or developing a new radiation sensitivity signature (Speers et al. 2013). Three prospective, single-arm clinical trials are investigating recurrence rates based on biologic identity, including luminal A disease (the LUMINA trial), a 21-gene recurrence score $\leq$18 (the IDEA trial), or based on the PAM50 gene expression signature (the PRECISION trial).

2.3 Ductal Carcinoma In situ

Ductal carcinoma in situ (DCIS) is a preinvasive process of the breast, in which the neoplastic lesion is confined to the ductal-lobular system though nonetheless possessing cytologic atypia with a predisposition toward malignant transformation (Lakhani et al. 2012). Owing to the recent increased utilization of mammography, DCIS has become a much more common diagnosis than in decades prior (Ernster et al. 1996). In the United States in 2014, there will be an estimated 62,570 new diagnoses of this disease compared to 232,670 new cases of invasive breast cancer (Siegel et al. 2014). Although not itself a cancerous lesion, several studies have examined the natural history of DCIS via clinical follow-up with women mistakenly diagnosed with benign disease on initial biopsy and without subsequent further treatment. These investigations found that breast cancer eventually develops in 39 to 53 % of such patients (Collins et al. 2005; Rosen et al. 1980; Sanders et al. 2005).

Given its substantial incidence as well as the possibility that DCIS might develop into frank malignancy, management of this disease has warranted careful deliberation on the part of the medical community. Historically, excellent rates of local control and overall survival were achieved with mastectomy. Although never examined in a prospective fashion, retrospective studies have demonstrated local recurrence rates of 3 % or less (Cutuli et al. 2001; Carlson et al. 2007; Kelley et al. 2011; Owen et al. 2013), and meta-analysis

has shown a recurrence rate of 1.4 % (Boyages et al. 1999). Similarly, rates of cause-specific survival have been excellent at 98 % or better (Kelley et al. 2011; Owen et al. 2013).

As mastectomy is an amputative procedure, it may represent too extensive a surgical approach for a disease that often does not progress to a cancerous condition. Concerns such as these have prompted investigation into whether lumpectomy – either alone or in combination with adjuvant radiotherapy – is adequate to address DCIS. Beginning in 1985, a total of four randomized trials have compared lumpectomy alone versus lumpectomy followed by radiotherapy in a broad range of patients (Wapnir et al. 2011; Bijker et al. 2001, 2006; Cuzick et al. 2011; Holmberg et al. 2008; Fisher et al. 1998, 1993; Julien et al. 2000; Houghton et al. 2003; Emdin et al. 2006; Pinder et al. 2010). Of note, these four trials – NSABP B-17, EORTC 10583, the UK/ANZ trial, and the SweDCIS trial – all included similar cohorts of patients: the majority in each trial were 50 years of age or older (67 to 93.5 % of patients) with mammographically detected small tumors (12.5–20 mm mean size) excised with negative margins (in 78–85 % of all cases). Areas of variability included the portion of women with high-grade lesions, ranging considerably from just 27 % of tumors in EORTC 10583 to 74.5 % in the UK/ANZ study (Bijker et al. 2001; Julien et al. 2000; Houghton et al. 2003; Pinder et al. 2010). Additionally, endocrine therapy was not routinely used in NSABP B-17, EORTC 10583, or the SweDCIS study, in contrast to the 2 × 2 factorial design of in the UK/ANZ study, in which tamoxifen was administered to 54 % of all patients (Houghton et al. 2003; Pinder et al. 2010). Unlike endocrine therapy, the approach to radiotherapy was rather uniform across trials: 50 gray (Gy) in 2 Gy daily fractions to the entire breast was the only regimen offered in NSABP B-17, EORTC 10853, and the UK/ANZ study, and this same approach was utilized in 80 % of radiotherapy patients in the SweDCIS study. Of note, boost techniques were infrequently employed, as these were not recommended in the UK/ANZ and SweDCIS studies and were performed in only 5–9 % of patients in the EORTC and NSABP trials, respectively (Wapnir et al. 2011; Bijker et al. 2001, 2006; Cuzick et al. 2011; Holmberg et al. 2008; Fisher et al. 1998, 1993; Julien et al. 2000; Houghton et al. 2003; Emdin et al. 2006; Pinder et al. 2010).

The results from these four trials were combined in an Early Breast Cancer Trialists' Collaborative Group individual patient-level meta-analysis (Correa et al. 2010). In all, outcomes from 3729 patients were analyzed. At a median follow-up of almost 9 years, radiotherapy roughly halved the rate of a woman developing an ipsilateral breast event (IBE), defined as either invasive disease or a recurrence of DCIS (rate ratio 0.46, $p < 0.00001$). The absolute risk reduction at 10 years was 28.1 % in the surgery-alone arm compared to 12.9 % in those that received radiotherapy. Radiotherapy was successful in reducing risk regardless of age, mode of detection (mammographic versus clinical), lumpectomy technique, margin status, focality, nuclear grade, histologic features, or subsequent tamoxifen use. Further, the proportional reduction was independent of all these factors except that it varied by age, as those women who were 50 years of age or older received a slightly larger benefit than those younger than 50 (rate ratios of 0.38 versus 0.69, respectively, $p = 0.0004$) (Correa et al. 2010).

Despite this profound reduction in disease recurrence, no survival benefit was detected: 10-year breast cancer mortality was 4.1 % in the radiotherapy arms versus 3.7 % in the surgery-alone arms. Likewise, 10-year overall survival was 8.4 and 8.2 %, respectively (Correa et al. 2010).

Finally, the authors of the meta-analysis examined a predefined subset of women thought to be at particularly low risk of local disease recurrence. This group of 291 patients included only those with negative margins as well as low-grade tumors, 20 mm or less in size. However, even for these women, radiotherapy conferred a highly significant benefit, reducing IBE rates at 10 years from 30.1 to 12.1 % (rate ratio 0.48, $p = 0.002$) (Correa et al. 2010).

Though this meta-analysis did not identify a subgroup of patients for whom radiation provided little or no benefit, the consistent finding

that such treatment does not confer a survival benefit – as well as its acute and long-term sequelae – has led to a continued efforts to identify low-risk women for whom omission of adjuvant radiotherapy might be appropriate.

One classification schema aimed at achieving this end was proposed by Silverstein et al. and is presently known as the University of Southern California/Van Nuys prognostic index (Silverstein et al. 1996; Silverstein 2003). In the creation of this index, outcomes from 706 DCIS patients were retrospectively analyzed. Of these patients, 426 were treated with surgery alone, while 280 were treated with excision as well as adjuvant radiation. On multivariate regression, four predictors of local recurrence were identified: tumor size, pathologic classification, margin width, and age. These categories were combined into a scoring system, in which each factor was assigned a value from 1 to 3, and the total prognostic score is the resultant sum (see Table 3). The authors recommend excision alone for women with a score of 4 to 6, excision followed by adjuvant radiotherapy for 7 to 9, and mastectomy for scores of 10 or greater. The recommendation that radiotherapy be omitted for those women in the lowest-risk category was a result of an observed 1 % IBE rate that was not impacted by radiotherapy (Silverstein 2003).

While promising, the broader applicability of a tool created from a modest sample of patients is limited by the extent to which it is externally validated in independent cohorts. Unfortunately, attempts at such validation have been inconsistent (Boland et al. 2003; MacAusland et al. 2007; Di Saverio et al. 2008; de Mascarel et al. 2000). Certain investigators have found that the Van Nuys prognostic index lacked meaningful discriminatory power (Boland et al. 2003; MacAusland et al. 2007), while others found a 12.7 % IBE rate in the low-risk population of women not treated with radiotherapy (de Mascarel et al. 2000).

Similarly, investigators from Memorial Sloan Kettering (MSK) have constructed a nomogram for recurrence risk based upon retrospective, single-institution data (Rudloff et al. 2010). However, the results of external and independent validation of this measure have been decidedly mixed (Collins et al. 2012; Sweldens et al. 2014; Yi et al. 2012). Given the lingering questions regarding validity, basing decisions regarding omission of treatment based upon either the University of Southern California/Van Nuys prognostic index or the MSK nomogram cannot be recommended at present.

Prospective attempts to identify a more suitable a low-risk population of DCIS patients have proceeded through three prospective trials (McCormick et al. 2012; Wong et al. 2014; Solin et al. 2013; Page et al. 1991; Hughes et al. 2009). The first of these investigations was a single-arm study at the Dana-Farber Cancer Institute that included only those women with low- or intermediate-grade DCIS, mammographic disease extent of 2.5 cm or less, and final surgical margins of at least 1 cm width (Wong et al. 2014, 2006). Endocrine therapy was not allowed. One hundred fifty-eight women enrolled, and after a median follow-up of 11 years for 158 patients, the 10-year IBE rate was 15.6 % (Wong et al. 2014). Nonetheless, it should be noted that the trial did allow enrollment of patients whose tumors exhibited a small number of DCIS cells with high-grade nuclei, and such high-grade lesions harbor a higher propensity for recurrence (Boyages et al. 1999; Solin et al. 1993).

ECOG 5194 was a multicenter, cooperative group single-arm study that also examined this issue, and it enrolled women with low- or intermediate-grade DCIS 2.5 cm or less in size or those with high-grade lesions that were 1 cm or less. Surgical margins of at least 3 mm were required as was a postoperative mammogram without residual calcifications. The study eventually enrolled 670 women. Slightly less than one-third of patients in each group received adjuvant tamoxifen. However, despite the rigorous entry criteria, the 10-year IBE rate was disappointingly high for both groups: 14.6 % in those with low- or intermediate-grade tumors and 19.0 % in those with high-grade tumors (Solin et al. 2013).

RTOG 98-04 was the most recently reported prospective study to attempt identification of a low-risk group of women. Unlike the Dana

Farber and ECOG 5194 studies, this was a randomized control trial (McCormick et al. 2012). Women were eligible for inclusion if they had low- or intermediate-grade tumors, 2.5 cm or less in size, and surgical margins of at least 3 mm. The randomization was between observation and adjuvant radiotherapy. A total of 636 patients enrolled, well short of the initial goal of 1790 patients, and the study was closed early due to poor accrual. Approximately two-thirds of women received adjuvant tamoxifen. After a median follow-up of 7.2 years, there was a large difference in local control between the two groups, with a 6.4 % IBE rate in the observation arm versus 0.9 % in the radiotherapy arm (McCormick et al. 2012).

These three studies have demonstrated the difficulty of utilizing histopathologic tumor characteristics and treatment factors to identify a low-risk population of women (McCormick et al. 2012; Wong et al. 2014; Solin et al. 2013; Hughes et al. 2009; Wong et al. 2006). This has prompted interest in developing genomic assays in order to better quantify recurrence risk. One such instrument is the Oncotype DX DCIS score, developed by Genomic Health Inc. through analysis of tumor samples obtained from almost half of the patients on ECOG 5194 (Solin et al. 2013). From these samples, the investigators constructed a 12-gene assay, consisting of a subset of those genes used in the better known 21-gene recurrence score that is commonly used to predict the recurrence risk for invasive breast cancers. This new assay was then able to stratify patients (from the same dataset used to construct the model) into low, intermediate, and high-risk categories, with corresponding 10-year risk of developing an IBE of 10.6, 26.7, and 25.9 %, respectively (Solin et al. 2013).

Nevertheless, concerns have been raised, including the fact that the test's low-risk group exhibited a high enough IBE rate that the assay might not identify a group with a meaningfully reduced risk of recurrence. On the other end of the risk spectrum, the test did not substantially differentiate between those with intermediate and high risk of any IBE, though it was able to distinguish these groups in terms of differing risks of developing an invasive recurrence (Solin et al. 2013).

Whether through genomic assays such as the Oncotype DX DCIS score or through the identification of clinicopathologic and treatment factors derived from retrospective and prospective investigations, efforts to define a subgroup of DCIS patients appropriate for omission of adjuvant treatment have fallen short of providing a single, simple answer. Rather, the evidence has consistently suggested benefit from adjuvant radiotherapy, and its use remains routine. If a woman desires to be treated with excision alone, the studies discussed herein should inform discussion and add to the clinician's repertoire of tools in the ongoing effort to properly individualize treatment.

2.4 Lobular Carcinoma In situ

Lobular carcinoma in situ (LCIS) is an uncommon lesion (Page et al. 1991; Akashi-Tanaka et al. 2000), which consists of a proliferation of noninvasive, non-cohesive, small epithelioid cells confined to the ductal-lobular system (Lakhani et al. 2012). Compared to women without such lesions, the presence of LCIS approximately doubles the relative risk of subsequently developing a histologically distinct invasive breast cancer in either breast (Page et al. 1991; Wheeler et al. 1974; Rosen et al. 1978; Chuba et al. 2005; Fisher et al. 2004). As such, this lesion is felt to be a marker of those at increased risk for invasive disease, rather than a direct precursor to breast cancer in and of itself. Given this, following excisional biopsy of LCIS to exclude the presence of concomitant malignancy, radiotherapy is not indicated.

In comparison to classic LCIS, pleomorphic lobular carcinoma in situ (PLCIS) is a less common lesion that exhibits clustered groupings of larger cells with abundant and granular cytoplasm (Eusebi et al. 1992; Middleton et al. 2000). In fact, it may also include areas of calcification and necrosis, similar in appearance to DCIS (Georgian-Smith and Lawton 2001). Given these similarities, PLCIS is most easily distinguishable from DCIS not on the basis of its histology but rather by its lack of E-cadherin expression on

immunohistochemical staining (Lakhani et al. 2012; Jacobs et al. 2001). Further, unlike LCIS, areas of PLCIS can contain components of morphologically similar though not frankly invasive disease (Bentz et al. 1998; Buchanan et al. 2008; Sneige et al. 2002), indicating that PLCIS might in fact be a true precursor of malignancy. This conclusion is bolstered by anecdotal evidence that women with excised PLCIS can experience recurrences, often of invasive cancer (Eusebi et al. 1992; Khoury et al. 2014). Given this, most believe that appropriate treatment for such patients is complete, margin-negative excision, followed by adjuvant radiotherapy. Still, prospective evidence in this arena is sorely lacking, and hence this recommendation awaits either confirmation or refutation by more thorough investigations.

3 Techniques and Approaches to Treatment

3.1 Hypofractionation

Radiotherapy delivered after breast-conserving surgery has conventionally involved dosages of 45–50 gray (Gy) to the entire breast – often followed by a boost to the lumpectomy cavity – given daily over a course of 5–6 weeks (Ceilley et al. 2005). Such an approach has yielded both excellent rates of disease control (Darby et al. 2011b), as well as satisfactory cosmetic results (Taylor et al. 1995; Vrieling et al. 1999). Nonetheless, preclinical studies have suggested that hypofractionated courses of radiation to a lower total dose – and hence over a shorter time course – might be just as effective (Cohen 1952; Douglas and Castro 1984). The motivation to shorten treatment delivery has stemmed from a desire to reduce imposed treatment burdens. In particular, it is difficult for many women to receive 5 or 6 weeks of traditional therapy: the inconvenience of numerous daily visits has been identified both as increasing the number of women who opt for mastectomy and as contributing to radiotherapy's lack of receipt after breast-conserving surgery (Morrow et al. 2001; Nattinger et al. 1992).

3.2 Hypofractionated Whole Breast Irradiation

One such approach to hypofractionation involves using a larger fraction size to treat the entire breast, rather than the 1.8 to 2.0 Gy most commonly employed in the past (Ceilley et al. 2005). While initial attempts to increase fraction size maintained the same total dosage as employed with conventional fractionation and hence resulted in significantly increased toxicity (Whelan et al. 2008), more modern trials have modified fractionation while using a lower total dose (Whelan et al. 2010; Haviland et al. 2013; Bentzen et al. 2008a, b; Owen et al. 2006).

Of these, the trial with the longest follow-up is a Canadian trial of accelerated whole breast irradiation (AWBI) reported by Whelan et al. (Whelan et al. 2010). This study enrolled women with small to moderate breast size, who, after lumpectomy as well as axillary lymph node dissection, were found to have pT1–2 pN0 disease. Negative margins were required and defined as no tumor on ink. Randomization was to 50 Gy in 25 fractions or 42.5 Gy in 16 daily fractions, and homogeneity of dose was allowed to vary by as much as 7 %. No boost was employed. In all, 1234 women were enrolled. Endocrine therapy was used in 41 % of women and chemotherapy in 11 %. At a median of a 12-year follow-up, there was no difference in overall survival (84.4 versus 84.6 %) or local recurrence rates (6.7 versus 6.2 %) between those who received conventional fractionation and hypofractionation, respectively (Whelan et al. 2010).

Importantly, rates of late toxicity were similar between the two arms, as were rates of good or excellent cosmesis, which were approximately 70 % in both arms. Even with this demonstration of equivalency between these two treatment approaches, adoption of hypofractionation has been limited (Ashworth et al. 2013; Bekelman et al. 2014; Jagsi et al. 2014a, b; Wang et al. 2014). There are several possible explanations for this, including a subset analysis reported in the initial publication, which showed that those with grade 3 disease were at an increased risk for local recurrence if they received hypofractionated treatment

(HR 3.08, $p = 0.01$) (Whelan et al. 2010). However, further exploration of this finding on subsequent central pathologic reevaluation of 989 of the total 1234 specimens demonstrated that high grade did not, in fact, significantly interact with treatment type (Bane et al. 2014). Similar findings that those with grade 3 disease are not adversely affected by hypofractionation have been seen in subsequent trials (Haviland et al. 2013). Other barriers to utilization might include concerns that rates of acceptable cosmesis in both arms were generally lower than that seen in American studies (Taylor et al. 1995), as well as the fact that this study did not utilize a boost, the benefit of which was confirmed after the trial was already completed (Bartelink et al. 2007). Finally, with rising rates of obesity impacting over a third of all women in the United States (Flegal et al. 2012), clinicians might be hesitant to adopt a technique that was investigated in those with limited body habitus and breast size (Whelan et al. 2010).

Confirmation of hypofractionation's utility has come from three trials performed in the United Kingdom (Haviland et al. 2013; Bentzen et al. 2008a, b; Owen et al. 2006). The first of these studies drew patients from the Royal Marsden Hospital and the Gloucestershire Oncology Center (Owen et al. 2006). It enrolled women who underwent lumpectomy and were found to have T1–3 N0–1 disease. Patients were randomized to 50 Gy in 25 fractions, 42.9 Gy in 13 fractions, or 39 Gy in 13 fractions. All regimens were delivered in a non-accelerated fashion over 5 weeks. The trial enrolled 1410 patients with a median follow-up of 9.7 years. The majority of women underwent endocrine therapy; chemotherapy was uncommon. Three-quarters of patients received a boost to the lumpectomy cavity in addition to their assigned whole breast regimen. Rates of local recurrence were not significantly different between the three arms: 12.1 % in the 50 Gy group, 9.6 % in the 42.9 Gy group, and 14.8 % in the 39 Gy group (Owen et al. 2006). In terms of cosmetic results, the 39 Gy arm fared best, with 72.3 % of patients free from long-term moderate to marked induration, compared to 63.7 % in the 50 Gy arm and 48.9 % in the 42.9 Gy arm (Yarnold et al. 2005).

The UK Standardization of Radiotherapy A (START A) trial randomized patients to 50 Gy in 25 fractions versus 41.6 Gy or 39 Gy, both in 13 fractions and delivered over a 5-week course (Haviland et al. 2013; Bentzen et al. 2008b). The trial enrolled 2236 women with a median follow-up of 9.3 years. Of note, over one-third of women in this trial received chemotherapy. Rates of local recurrences were not significantly different between arms: 7.4 % in the standard fractionation arm versus 6.3 and 8.8 % in the 41.6 and 39 Gy arms, respectively. Photographic evaluations of breast appearance showed superior cosmetic results in the 39 Gy arm compared to standard fractionation (HR 0.69, $p = 0.01$), though those who received a boost had worse outcomes in this regard (Haviland et al. 2013).

The START B trial randomized women to 50 Gy in 25 fractions versus 40 Gy in 15 fractions, delivered on an accelerated scheduled over 3 weeks (Haviland et al. 2013; Bentzen et al. 2008a). It enrolled 2215 patients and rates of local recurrence were not significantly different between the two groups (5.5 % in the standard fractionation arm and 4.3 % in the AWBI arm). Rates of moderate to marked breast shrinkage, telangiectasia, and breast edema were significantly lower in the 40 Gy arm (Haviland et al. 2013).

Given the available data, in 2011 ASTRO issued guidelines as to which women are particularly appropriate candidates for AWBI: those who are 50 years of age or older, with T1–2 N0 disease, not requiring chemotherapy, and whose radiotherapy plan achieves dose inhomogeneity of 7 % or less. The authors favored a regimen of 42.5 Gy in 16 fractions (Smith et al. 2011a).

Ongoing avenues of investigation include the FAST trial in the United Kingdom, which is comparing 30 Gy and 28.5 Gy – both delivered in 5 fractions over 5 weeks – to more conventionally fractionated treatment (Agrawal et al. 2011). Likewise, the FAST-Forward trial compares 26 and 27 Gy delivered over 1 week in 5 daily fractions versus 40.05 Gy in 15 fractions over 3 weeks. Finally, RTOG 1005 investigates reducing treatment time by incorporating a simultaneous integrated boost given via intensity-modulated radiotherapy (IMRT) based on favorable

outcomes from an earlier Phase II study (Freedman et al. 2007). Data from these trials require further maturation until the full promise of these regimens is known.

3.3 Accelerated Partial Breast Irradiation

Accelerated partial breast irradiation (APBI) is a developing alternative to whole breast irradiation (WBI). Theoretically, there are several potential advantages to APBI that have motivated research into refining its delivery. First, APBI has the potential to further reduce treatment times, making the receipt of radiotherapy more convenient, a possibility that is particularly important for those living in rural areas in which the distance to the nearest treatment facility can limit therapeutic options (Schroen et al. 2005). Further, by limiting the target volume to the lumpectomy cavity and immediately surrounding tissue, APBI may reduce the dose delivered to the nearby organs at risk, such as the heart, lung, and ribs (Moran et al. 2009; Rusthoven et al. 2008; Taghian et al. 2006a). Such an advantage might be of clinical importance in limiting late radiation-induced toxicities and is of particular note given the recent attention paid to radiotherapy-related cardiac disease (Darby et al. 2013a). Nonetheless, these dosimetric advantages may be offset by other concerns regarding toxicity and cosmesis (Olivotto et al. 2013; Liss et al. 2014; Jagsi et al. 2010; Hepel et al. 2009; Leonard et al. 2013).

In terms of disease control, irradiating only the area about the tumor bed may be reasonable in selected patients, given that this is the area most at risk for the development of a local recurrence (Clark et al. 1992; Liljegren et al. 1999b; Vicini et al. 2003a). Additionally, it may be possible to predict which patients are at low risk of harboring residual disease elsewhere in the breast, far from the surgical site (Vicini et al. 2004). Despite this, concerns remain as to whether APBI is truly adequate in this regard, as some researchers have found that microscopic disease may exist far from the initial lumpectomy cavity and that local recurrences can affect such distant portions of the breast (Veronesi et al. 2001b; Holland et al. 1985; Vaidya et al. 1996; Morimoto et al. 1993).

There are several techniques of APBI, the first of which is multicatheter interstitial brachytherapy. One of the earliest studies utilizing this approach is from Guy's Hospital in London. In this series of 27 patients implanted with iridium-192, 55 Gy was delivered over a course of 5 days (Fentiman et al. 1991, 1996). Unfortunately, ten patients experienced local failure, perhaps due to the inadequate patient selection and a lack of more sophisticated dosimetry in this early era. However, more recent investigations have yielded promising results. Prospective studies in the United States and Europe have enrolled older women (median age 60–65), with small tumors (median size 0.9–1.5 cm) and with estrogen receptor-positive disease (65–100 % of cases) (Kuske et al. 2006; Arthur et al. 2008; Rabinovitch et al. 2014; Ott et al. 2007; Garsa et al. 2013; Kaufman et al. 2007; Antonucci et al. 2009; King et al. 2000; Polgár et al. 2007, 2013; Aristei et al. 2013, 2009). Few women had evidence of nodal involvement, ranging from 0 to 19 % of participants. These studies have a follow-up of approximately 5 to 10 years and have shown excellent local control, as rates of ipsilateral breast events have ranged from 2 to 6 % (Kuske et al. 2006; Arthur et al. 2008; Rabinovitch et al. 2014; Ott et al. 2007; Garsa et al. 2013; Kaufman et al. 2007; Antonucci et al. 2009; King et al. 2000). The only outlier in terms of recurrence rate is a randomized Hungarian study that reported local failures in 9 % of patients, though this was no different than that observed in the WBI control arm (Polgár et al. 2007, 2013). Additionally, multicatheter brachytherapy has often shown good cosmetic outcomes, with acceptable results in 66 to 98 % of patients (Rabinovitch et al. 2014; Ott et al. 2007; Garsa et al. 2013; Kaufman et al. 2007; King et al. 2000; Polgár et al. 2013; Aristei et al. 2013, 2009). Nonetheless, conclusions regarding cosmesis are tempered by long-term results from other investigators, who have found moderate to severe fibrosis in over half of patients after 12 years of follow-up, raising significant concerns about this technique as applied in that era (Hattangadi et al. 2012).

From these studies, it is clear that multicatheter brachytherapy has demonstrated durable long-term results in selected patients, though its broader adoption may have been hampered by the invasiveness of the procedure, as well as its technical complication and clinician dependence. Further insight will come from a recently closed GEC-ESTRO randomized study that was open to women with early-stage invasive disease or DCIS. This trial enrolled 1195 women, who were randomized to standard WBI versus multicatheter APBI: either high-dose rate brachytherapy (32 Gy in 8 fractions or 30.3 in 7 fractions) or pulsed dose rate brachytherapy (50 Gy at 0.6 to 0.8 Gy per hour). Results have not yet been reported.

In contrast to the technical demands of the multicatheter approach, single entry, intracavitary brachytherapy is less dependent on clinician expertise and was initially developed as the single-lumen MammoSite device for use with iridium-192. The most extensive report on outcomes with this technique is from an analysis of the prospective American Society of Breast Surgeons MammoSite Registry Trial (Shah et al. 2012; Vicini et al. 2006). The trial enrolled 1961 patients, and the 5-year rate of local recurrence was 2.9 % (Shah et al. 2012). At 3 years, 90 % of women were judged to have good or excellent cosmetic outcomes (Vicini et al. 2006), which is comparable to findings from other studies (Benitez et al. 2007; Vargo et al. 2014).

Despite these results, a recent Medicare claims analysis has raised significant concerns about single-lumen, intracavitary brachytherapy (Smith et al. 2012). In this retrospective, population-based study of 92,735 women diagnosed with breast cancer between 2003 and 2008, 6952 women treated with brachytherapy were compared to 85,783 women treated with WBI. Those who received brachytherapy had approximately twice the risk of undergoing a subsequent mastectomy, with a 5-year rate of 3.95 % compared to 2.18 % of those who received external beam radiation (HR 2.19, $p < 0.001$). Further, the brachytherapy group experienced significantly greater rates of postoperative complications, rib fracture, and long-term breast pain (Smith et al. 2012). Of note, this study reflects the early experience with brachytherapy, prior to the development of more thorough criteria for patient selection (Smith et al. 2009), and thus it might not represent the technique as currently practiced (Cuttino et al. 2012). It remains to be seen whether refinement of the intracavitary technique through the use of recently developed multilumen catheters and better dosimetric planning will improve long-term toxicity rates (Arthur et al. 2013; Lu et al. 2012; Yashar et al. 2011; Manoharan et al. 2010), though early results from a registry trial are promising (Cuttino et al. 2014). Finally, concerns regarding toxicity may be clarified by results from RTOG 0413/ NSABP B-39, which is a randomized trial comparing WBI to a variety of APBI techniques, although only a minority received brachytherapy. Outcomes from this study are pending, and it is discussed in more detail later in the chapter.

Another option for the delivery of APBI is through the use of conformal external beam radiotherapy, an approach facilitated by the emergence of improved targeting and dosimetry. Two early randomized studies have compared external beam partial breast irradiation to more conventional, whole breast treatment (Ribeiro et al. 1990, 1993; Dodwell et al. 2005). The largest of these trials was undertaken at the Christie Hospital in Manchester, England (Ribeiro et al. 1990, 1993). Its enrollment criteria allowed for women less than 70 years old, with tumors less than 4 cm, and a clinically negative axilla. Margins following lumpectomy were required to be macroscopically uninvolved. The trial enrolled 708 women. APBI was given via an en face electron beam to 40 to 42.5 Gy in 8 fractions, compared to WBI, which consisted of 40 Gy in 15 fractions. After a median follow-up of 65 months, 14 % of those in the APBI arm experienced a local recurrence, compared to 6 % in the WBI arm. Cosmetic outcomes were also worse in the APBI group (Ribeiro et al. 1993). Likewise, a randomized study from Leeds Hospital in Yorkshire randomized 174 early-stage patients (Dodwell et al. 2005). The partial breast arm consisted of treatment with either photons or electrons, delivered to 50 Gy in 20 fractions, via an

en face or tangential technique. The WBI group received 40 Gy in 15 fractions with a corresponding nodal treatment. Similar to the study from Christie Hospital, after 8 years of follow-up, those in the APBI arm had a 24 % locoregional recurrence rate compared to 9 % in the WBI arm (Dodwell et al. 2005). No cosmetic outcomes were reported.

Subsequent investigators have refined patient selection and used more sophisticated planning and lower dosages to pursue external beam APBI. Physicians at New York University have reported on their experience with APBI, which utilized 30 Gy in five fractions over 10 days delivered to a prone patient via parallel-opposed minitangents (Formenti et al. 2012; Wernicke et al. 2006; Osa et al. 2014). Five-year results have been encouraging, with a less than 1 % local failure rate, as well as excellent or good cosmesis in 89 % of patients (Formenti et al. 2012). As opposed to this prone technique, radiation oncologists at Beaumont Hospital developed the use of external beam APBI with the patient in the supine position. This approach utilized four or five noncoplanar photon beams to deliver 34 to 38.5 Gy in ten fractions (Vicini et al. 2003b, 2007; Shah et al. 2013a). Results have been favorable, with no local recurrences and excellent cosmesis in 81 % of patients at 5 years (Shah et al. 2013a). Likewise, 38 Gy in in ten BID fractions was utilized in RTOG 0319, which was a Phase I/II feasibility trial that enrolled 58 patients (Vicini et al. 2010). Early results have shown a 6 % in-breast recurrence rate at 4.5 years of median follow-up, and only two patients developed grade 3 skin toxicity. Although this low rate of toxicity is promising, it did not correlate with cosmetic outcomes. When radiation oncologists participating in the study assessed cosmesis, the rate of fair or poor outcomes was substantial and increasing over time: 26 % of patients had unacceptable cosmesis at 1 year posttreatment, compared to 42 % at 3 years (Chafe et al. 2013).

In terms of efficacy, other prospective single institution studies have found excellent rates of local control (Pashtan et al. 2012; Rodríguez et al. 2013; Lei et al. 2013; Berrang et al. 2011). While these studies have shown acceptable cosmesis (Rodríguez et al. 2013; Lei et al. 2013; Berrang et al. 2011; Galland-Girodet et al. 2014), cautionary cosmetic outcomes have been reported not just from RTOG 0319 as discussed above (Chafe et al. 2013) but also from Tufts University and the University of Michigan (Liss et al. 2014; Jagsi et al. 2010; Hepel et al. 2009; Leonard et al. 2013).

These concerns regarding cosmesis have received renewed attention with the publication of interim results from the multicenter Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) in Canada (Olivotto et al. 2013). This study randomized women to either WBI (either 42.5 Gy in 16 fractions or 50 Gy in 25 fractions, followed by a boost at the discretion of each participating center) or external beam APBI delivered to a total dose of 38.5 Gy in ten BID fractions over a course of 5 to 8 days. No boost was allowed in the APBI arm. Appraisal of cosmesis was extensive: evaluations were performed by patients, nurses, and physicians. Patients evaluated their own cosmetic outcomes using a validated breast cancer questionnaire (Whelan et al. 2000a; Levine et al. 1988). Nurses were trained using an EORTC module and rating system designed specifically for cosmetic evaluation of women who had undergone treatment for breast cancer (Aaronson et al. 1988). Finally, two different panels of physicians assessed cosmesis at 3 years by examining digital photographs of patients. Notably, these panels were blinded to each patient's treatment arm. Toxicity was captured using the Common Toxicity Criteria for Adverse Events (CTCAE) (Olivotto et al. 2013).

RAPID has closed to accrual after enrolling 2135 women with a median follow-up of 36 months. Rates of adverse cosmesis at 3 years were significantly worse in the APBI arm as compared to the WBI arm, whether judged by the patients themselves (26 versus 18 %, $p = 0.0022$), trained nurses (29 versus 17 %, $p < 0.001$), or a physician panel (35 versus 17 %, $p = 0.001$). Interestingly, poor cosmesis did not correlate strongly with CTCAE, as the rate of grade 3 or greater toxicity was only 1.4 % in the APBI group. The lack of correspondence between cosmetic outcomes and CTCAE has been prospectively documented by others (Liss et al. 2014; Jagsi

et al. 2010; Chafe et al. 2013) and calls into question the sensitivity of this scale in capturing cosmetically meaningful data. More so, this underscores the need to develop validated measures of acute toxicity (Shumway et al. 2014), as well as more thorough methods of evaluating cosmesis (Aaronson et al. 1988). Finally, cosmetic outcomes in the APBI arm have continued to worsen over the entire period of follow-up. For instance, at the 3-year mark, 33 % of APBI patients were rated by nurses as having adverse cosmesis, but this increased to 37 % at 5 years (Olivotto et al. 2013). A similar worsening of cosmesis over time was seen in both RTOG 0319 and the University of Michigan experience (Liss et al. 2014; Chafe et al. 2013).

There are several possible explanations for these poor outcomes, and the topic has been well discussed by the authors of the RAPID study and others (Olivotto et al. 2013; Liss et al. 2014; Jagsi and Haffty 2013). First, external beam APBI – as compared to other techniques – may result in a higher integral dose to the breast (Weed et al. 2005). Though RAPID is limited to less than 35 % the volume of breast that could receive 95 % of the prescription dose, this may still be too high. Likely, more sophisticated dose constraints will be required in order to avoid adverse outcomes, as evidenced by several investigations that have shown a dose-volume relationship with cosmesis (Liss et al. 2014; Hepel et al. 2009; Leonard et al. 2013). Further, both biological modeling and clinical findings have suggested that cosmetic outcomes of the breast may be disproportionately affected by large fraction sizes unless there is a corresponding reduction in total dose delivered (Bentzen et al. 2008a, b; Yarnold et al. 2005, 2011). This may be particularly true with twice-daily fractionation, as normal breast tissue might not have enough time to repair itself (Bentzen and Yarnold 2010).

As an aside, though these poor cosmetic results are concerning, outcomes derived from patients treated with external beam radiotherapy cannot be extrapolated to APBI delivered via brachytherapy, which has typically delivered radiation more conformally, to smaller volumes (Ott et al. 2007; Kaufman et al. 2007; Aristei et al. 2013; Vicini et al. 2006; Benitez et al. 2007; Vargo et al. 2014).

Ongoing questions regarding cosmesis outcomes with external beam approaches to APBI may be answered by RTOG 0413/ NSABP B-39, which is a randomized study of standard WBI versus APBI for women with DCIS or early-stage breast cancer. This trial closed to accrual in 2013, after enrolling 4311 patients. Those in the APBI arm could receive any of three various approaches to adjuvant treatment, either multicatheter interstitial brachytherapy, intracavitary brachytherapy, or external beam radiotherapy, but the vast majority of patients enrolled received external beam treatment. Though there have been reportedly low rates of CTCAE-graded toxicity (Wolmark et al. 2010), this correlates poorly with cosmetic outcomes, as discussed earlier (Olivotto et al. 2013; Liss et al. 2014; Jagsi et al. 2010). Therefore, no conclusion can be made regarding cosmesis in this trial until further data are released. Regarding the efficacy of APBI, this study will hopefully address whether it is truly comparable to WBI and for which subpopulations it might be appropriate, as it has enrolled substantial numbers of women younger than age 50, as well as patients with hormone receptor-negative disease or DCIS.

Two additional randomized trials of external beam partial breast irradiation versus WBI were recently closed. The first of these was opened at the University of Florence in 2005, and it randomized 520 women between APBI delivered with IMRT to 30 Gy in five fractions and WBI with 50 Gy in 25 fractions (Livi et al. 2010). Five-year outcomes have shown good to excellent cosmesis in over 90 % of patients in both arms, as well as equivalent disease control. However, longer follow-up is needed to see if these results are durable (Livi et al. 2014). The second study is the IMPORT-LOW study performed by the UK Medical Research Council. This included 2100 women, randomized to partial breast irradiation with IMRT to 40 Gy in 15 fractions versus WBI radiation to 36 Gy along with a simultaneous boost to the lumpectomy cavity of 40 Gy, delivered in 15 fractions. Results have not yet been reported.

One niche modality of external beam APBI that deserves mention is intraoperative radiotherapy (IORT), in which a woman is treated with radiation during her lumpectomy procedure,

thus maximizing her convenience and theoretically obviating the need for further, prolonged adjuvant radiotherapy. Unfortunately, outcomes with this technique have been less than promising (Vaidya et al. 2010, 2014; Kimple et al. 2011; Vanderwalde et al. 2013; Veronesi et al. 2013). The largest of these studies is the TARGIT-A trial, which randomized 2232 patients to APBI versus WBI. The experimental arm utilized 50 kilovolt photons to deliver a single dose of 20 Gy to the lumpectomy bed (with a rapid falloff of dose to 5 to 7 Gy at 1 cm) (Vaidya et al. 2002, 2001). Of note, even in those women randomized to APBI, 14 % subsequently required WBI due to unfavorable pathologic features. At 5 years, the rate of local recurrence was 3.3 % in the intraoperative group versus 1.3 % in those who received more standard treatment (Vaidya et al. 2014). Similarly, the ELIOT trial has also reported sobering outcomes (Veronesi et al. 2013). This study enrolled 1300 women, randomized to standard WBI versus IORT delivered via an electron beam to a dose of 21 Gy at the applicator surface. Five-year rates of local recurrence were 1 % in the WBI arm versus 5 % in those that received IORT (Veronesi et al. 2013). These two randomized studies are consistent with the results of a smaller investigation from the University of North Carolina, which employed intraoperative electron therapy to give a single 15 Gy fraction. Rates of ipsilateral breast events were 15 % at 6 years (Kimple et al. 2011; Vanderwalde et al. 2013).

Such high rates of local failure serve to highlight the need for careful patient selection when using emerging and novel techniques. To assist clinicians with this task as more mature randomized data accumulate, several consensus guidelines have been published that detail the patient and disease characteristics that define an appropriate group for receipt of APBI off protocol, as the evidence accumulates (Smith et al. 2009; Arthur et al. 2003; Shah et al. 2013b). Among these, the 2009 ASTRO guidelines are perhaps most widely used and are presented in Table 2 (Smith et al. 2009). In any case, given the evolving nature of evidence for APBI in comparison to the wealth of high-quality data for more standard approaches, patients who desire to receive partial breast irradiation should be informed of any available clinical trials and encouraged to participate when appropriate.

Table 2 ASTRO consensus criteria for selection of patients "suitable" for partial breast irradiation off protocol

Factor	Criterion
Patient factors	
Age	≥60 y
BRCA1/2 mutation	Not present
Pathologic factors	
Tumor size	≤2 cm[a]
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No[b]
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2.0 cm[c]
Histology	Invasive ductal or other favorable subtypes[d]
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i^-, i^+)
Nodal surgery	SN Bx or ALND[e]
Treatment factors	
Neoadjuvant therapy	Not allowed

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Criteria are derived from data (when available) and conservative panel judgment

Abbreviations: *APBI* accelerated partial breast irradiation, *LVSI* lymphovascular space invasion, *ER* estrogen receptor, *DCIS* ductal carcinoma in situ, *EIC* extensive intraductal component, *LCIS* lobular carcinoma in situ, *SN Bx* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

[a]The size of the invasive tumor component as defined by the American Joint Committee on Cancer and referenced in Greene et al. (2002)

[b]The finding of possible or equivocal LVSI should be disregarded

[c]Microscopic multifocality is allowed, provided the lesion is clinically unifocal (a single discrete lesion by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) does not exceed 2 cm

[d]Favorable subtypes include mucinous, tubular, and colloid

[e]Pathologic staging is not required for DCIS

Table 3 Scoring system for the University of Southern California/Van Nuys prognostic index

Score	Size (mm)	Margin width (mm)	Pathology	Age (years)
1	≤15	≥10	Grade 1 or 2 without necrosis	>60
2	16–40	1–9	Grade 1 or 2 with necrosis	40–60
3	≥41	<1	Grade 3	<40

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3.4 IMRT

Whole breast radiation has traditionally been delivered with tangent beams and use of simple wedges to improve homogeneity. However, due to the complex three-dimensional shape of the breast, conventional two-dimensional techniques are often unable to deliver a homogenous dose throughout the breast, resulting in substantial areas receiving excessive dose (known as "hot spots"). These hot spots may lead to acute and late toxicity.

With development of three-dimensional planning techniques, use of multileaf collimators and segmental blocking allow for differential attenuation of the radiation beam to significantly improve homogeneity throughout the breast. Rather than employing two opposed tangential fields, treatment is delivered using several segmented fields, often described as a step-and-shoot IMRT or "field-in-field" technique. This relatively simple "breast IMRT," which has the objective of improving homogeneity, should be distinguished from the more complex inverse-planned beamlet IMRT that is used to improve dose conformality.

Use of simple IMRT for whole breast radiation has been found to be dosimetrically superior to treatment techniques that employ only wedges and has been associated with reduced acute radiation dermatitis, edema, hyperpigmentation, and minimal late toxicity (Keller et al. 2012; Harsolia et al. 2007). Three randomized trials revealed improvement in acute and late effects of radiation with the use of breast IMRT. A Canadian study that randomized 358 patients to standard wedged technique versus breast IMRT observed a reduction in hot spots (5 % or higher hot spot decreased from 16.9 % of breast volume to 7.7 %), which corresponded with a significant decrease in moist desquamation from 47.8 % to 31.2 %, respectively (Pignol et al. 2008). Two prospective British trials reported improvements in long-term cosmesis with breast IMRT, assessed primarily using serial photographs (Donovan et al. 2007; Mukesh et al. 2013). Patients with large breast size were most likely to benefit from IMRT (Pignol et al. 2008; Mukesh et al. 2013). Thus, while there is strong evidence to suggest that breast IMRT decreases acute and late toxicity compared to conventional techniques, controversy remains regarding whether this treatment should be reimbursed at substantially higher IMRT levels or at levels closer to historical standards (Haffty et al. 2008; Smith et al. 2011b; Roberts et al. 2013) (Fig. 1).

4 Locally Advanced Breast Cancer

4.1 Postmastectomy Radiotherapy

Even after mastectomy and systemic therapy, occult disease may remain in the chest wall and regional lymph nodes, which if left untreated, could serve as a reservoir for distant tumor spread. By eliminating residual locoregional disease, postmastectomy radiation may therefore not only prevent morbid local recurrences but also has potential to reduce breast cancer-related mortality. However, not all patients have the same risk of harboring residual locoregional disease. Patients who are most likely to benefit from postmastectomy radiation are those with an isolated site of residual locoregional disease after mastectomy and systemic therapy or those with micrometastatic distant disease that is effectively eliminated with systemic therapy. Appropriate patient selection to identify which patients are likely to benefit from postmastectomy radiation has therefore been a key subject of controversy and research.

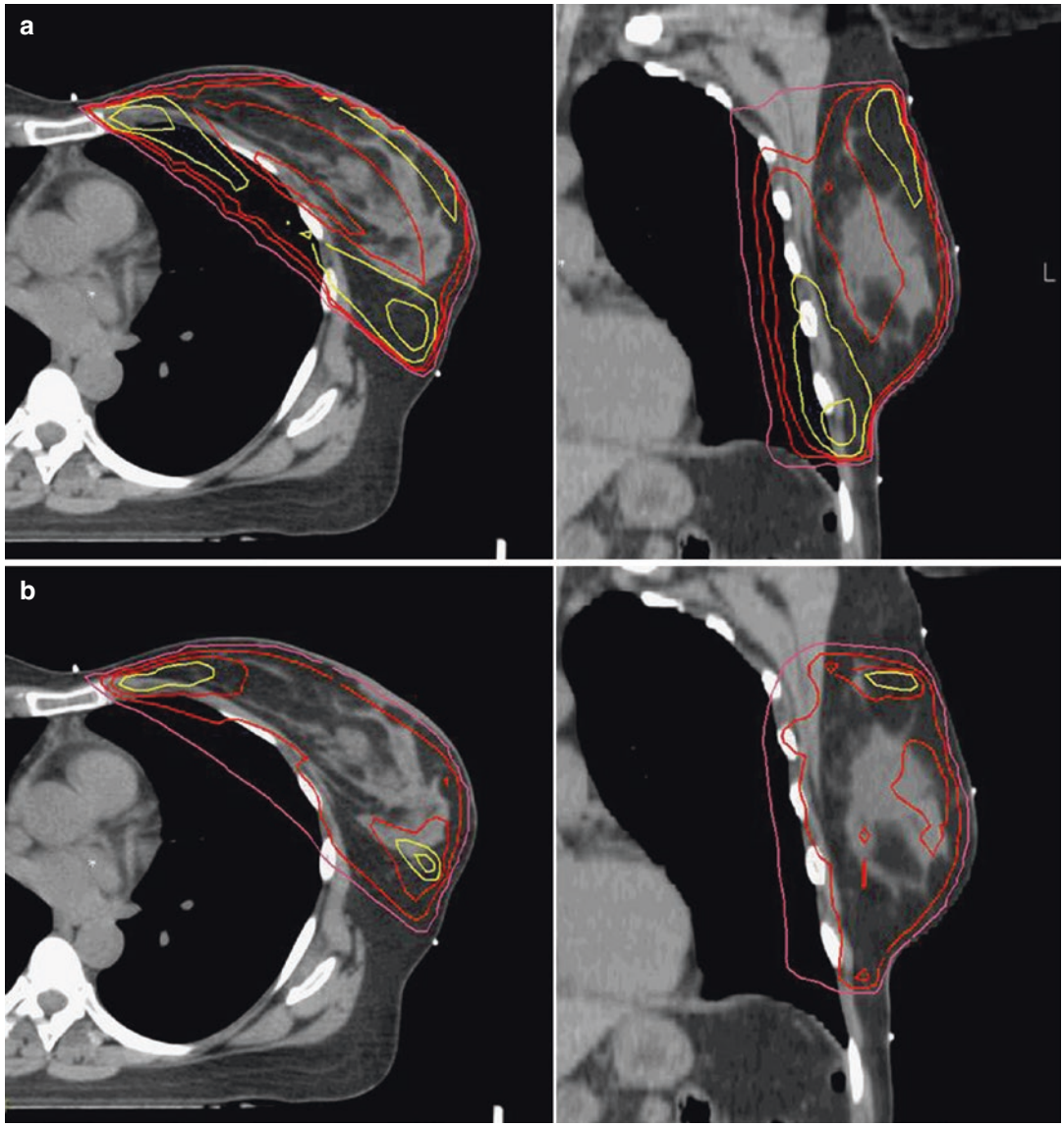

Fig. 1 (**a**) Simple tangential breast radiotherapy using a wedge. *Yellow* isodose lines depict areas receiving ≥107 % of the prescribed dose. (**b**) Segmented breast intensity modulated radiotherapy

Early trials of postmastectomy radiation consistently demonstrated a reduction in the rate of locoregional failure without improvement in overall survival (Early Breast Cancer Trialists' Collaborative Group 1995; Early Breast Cancer Trialists' Collaborative Group 2000; Pierce 2005). Prevention of locoregional recurrence after mastectomy is critical, as many patients subsequently develop distant disease and many locoregional recurrences cannot be successfully salvaged (Bedwinek 1994; Willner et al. 1997). Following mastectomy, systemic therapy reduces the rate of locoregional failure, though in many node-positive series, the risk of isolated locoregional failure remains 10 to 15 % or higher, even with the use of dose-dense anthracycline-based chemotherapy (Pierce 2005). Meta-analyses of several early trials investigating the role of postmastectomy radiation in conjunction with chemotherapy demonstrated that the benefit in disease control

was offset by treatment-related toxicity, likely related to exposure of large volumes of the heart and lungs to high doses of radiation (Early Breast Cancer Trialists' Collaborative Group 1995; Early Breast Cancer Trialists' Collaborative Group 2000; Cuzick et al. 1987; Cuzick et al. 1994). Only more recently, with development of more sophisticated radiation planning techniques and more effective systemic therapy, has the survival benefit become apparent (Clarke et al. 2005; Van de Steene et al. 2000; Whelan et al. 2000b). Trials of postmastectomy radiation from Denmark and British Columbia, which included largely lymph node-positive patients and a smaller number of individuals with locally advanced, lymph node-negative disease, revealed a substantial improvement in locoregional control, as well as a modest overall survival benefit, and serve as the foundation of existing clinical practice guidelines (NCCN 2014).

In a Danish trial of premenopausal patients with high-risk stage II or III breast cancer, 1708 patients were randomized to nine cycles of cyclophosphamide, methotrexate, and fluorouracil or eight cycles with postmastectomy radiation (Overgaard et al. 1997). After 9.5 years, postmastectomy radiation significantly reduced the frequency of locoregional recurrence from 32 to 9 % and improved overall survival from 45 to 54 % ($p < 0.001$). Multivariate analysis indicated that the benefit of postmastectomy radiation was applicable to all subgroups, regardless of tumor grade, size, or number of positive nodes. In the Danish 82c trial of postmenopausal patients, 1375 women who underwent modified radical mastectomy and received 1 year of adjuvant tamoxifen were randomized to postmastectomy radiation (Overgaard et al. 1999). After 10.3 years, locoregional recurrence decreased significantly from 35 to 8 %, and overall survival improved from 36 to 45 % ($p = 0.03$). Similarly, a 20-year follow-up of a Canadian study of 318 premenopausal patients with node-positive breast cancer who were treated with modified radical mastectomy and cyclophosphamide, methotrexate, and 5-fluorouracil revealed that postmastectomy radiation significantly reduced rates of both locoregional and systemic recurrence, resulting in substantially improved breast cancer-specific and overall survival (Ragaz et al. 2005).

Meta-analyses that included these more recent trials consistently demonstrated a two-thirds reduction in locoregional failure with the addition of postmastectomy radiation and confirmed the improvement in overall survival (Clarke et al. 2005; Whelan et al. 2000b). In a landmark publication from the EBCTCG in 2005 that included data from 8505 individual patients with positive lymph nodes, postmastectomy radiation decreased locoregional recurrence at 5 years from 22.8 to 5.8 %, resulting in a reduction of breast cancer mortality at 15 years from 60.1 to 54.7 % (absolute risk reduction 5.4 %) and all-cause mortality from 64.2 to 59.8 % (absolute risk reduction 4.4 %), all of which were statistically significant (Clarke et al. 2005). These findings led to the observation of a 4:1 ratio of absolute effects, such that for every four recurrences prevented after 5 years, one breast cancer death was avoided at year 15.

Although the Danish and British Columbia studies were influential in shifting opinion in favor of postmastectomy radiation, these studies met with criticism regarding their generalizability to the current era due to the use of older, low dose-intensity methotrexate-based chemotherapy (82b and Canadian studies) and use of tamoxifen for only 1 year (82c) and inadequate axillary surgery. In the Danish 82b and 82c trials, 62.6 % of patients had seven or fewer lymph nodes removed (Overgaard et al. 2007), likely resulting in underestimation of the true number of positive nodes and potential residual disease in the axilla due to inadequate resection (Iyer et al. 2000). Patients categorized as having one to three involved lymph nodes in the Danish trials might have been characterized as having four or more involved lymph nodes if a more complete axillary lymph node dissection had been performed. This inability to correctly identify patients with one to three involved lymph nodes may partially account for the observation of a higher rate of locoregional failure in the Danish and British Columbia studies (30–33 %) compared to other large cooperative groups (13–20 %) (Taghian et al. 2004a; Recht et al. 1999; Wallgren et al. 2003; Katz et al.

2000; Truong et al. 2005). Additionally, the rate of axillary failure without radiation in the Danish trials (13 %) (Overgaard 1999) was markedly higher compared to other cooperative groups (2.7–3.8 %) (Recht et al. 1999; Wallgren et al. 2003). Given these findings, it has been unclear to what extent the observed benefit of radiotherapy in these trials was a result of compensation for suboptimal surgery and/or suboptimal systemic therapy, particularly in patients with one to three positive lymph nodes. Consensus guidelines have uniformly recommended postmastectomy radiation for patients with ≥4 positive lymph nodes, but have tended to be more equivocal for patients with one to three involved lymph nodes (NCCN 2014; Harris et al. 1999; Recht et al. 2001; Taylor et al. 2000).

In response to these concerns, Danish investigators completed a pooled reanalysis of 1152 (37 %) patients from 82b and 82c with ≥8 lymph nodes removed (Overgaard et al. 2007). Though the absolute risk reduction in locoregional failure was smaller in patients with one to three positive lymph nodes compared to those with ≥4 involved nodes (41 % vs 23 %, respectively), both groups derived a similar absolute overall survival benefit from radiotherapy (9 %). The authors reason that patients with fewer involved lymph nodes, despite obtaining a relatively smaller absolute benefit in locoregional control, might be more likely to obtain a survival benefit from postmastectomy radiation due to a lower risk of distant metastasis. While patients with many involved lymph nodes may obtain a large reduction in locoregional failure, only a small proportion of these can obtain a survival benefit due to the high risk of distant metastasis. These observations, along with demonstration of a survival benefit in patients with one to three lymph nodes in the British Columbia trial (in which a median of 11 axillary lymph nodes were removed) (Ragaz et al. 2005), lend support for the role of postmastectomy radiation in patients with one to three involved lymph nodes. Most recently, an EBCTCG meta-analysis including 8135 individual patients from 22 prospective trials specifically investigated the role of postmastectomy radiation in patients with one to three positive lymph nodes. In the 1133 women with axillary lymph node dissection and one to three positive nodes who received systemic therapy, postmastectomy radiation reduced locoregional recurrence and significantly improved breast cancer-specific survival (McGale et al. 2014). In light of these data, guidelines from the National Comprehensive Cancer Network recommend that patients treated with mastectomy who are found to have one to three positive axillary lymph nodes should "strongly consider" postmastectomy radiation (NCCN 2014). The ongoing SUPREMO study, in which patients with T1–T2 tumors and one to three involved lymph nodes are randomized to postmastectomy radiation, may ultimately provide additional information in patients treated with contemporary systemic therapy (Russell et al. 2009).

Patients with negative axillary lymph nodes and certain high-risk features might also benefit from postmastectomy radiation. The Danish trials of postmastectomy radiation included patients with tumors >5 cm with negative axillary lymph nodes (Overgaard et al. 1997, 1999). Postmastectomy radiation significantly reduced locoregional recurrences in both pre- and postmenopausal patients at a 10-year follow-up and was associated with improved overall survival in premenopausal patients. However, the incidence of local failure in these node-negative patients without postmastectomy radiation was much higher in Danish trials (17 to 23 %) than in results from retrospective analyses of patients treated in NSABP trials (7.1 %) (Taghian et al. 2006b) and several other institutions (7.6–11 %) (Floyd et al. 2006; Mignano et al. 2007), leading to the conclusion that postmastectomy radiation may not be routinely indicated by tumor size alone.

The decision on whether to offer postmastectomy radiation to patients with T3 N0 disease can perhaps be further informed by retrospective studies of lymph node-negative patients with smaller primary tumors who were treated with mastectomy. These studies identified several risk factors associated with increased risk of locoregional recurrence, including lymphovascular invasion, higher grade, close or involved margins, larger tumor size, premenopausal status,

and omission of systemic therapy (Wallgren et al. 2003; Truong et al. 2005; Jagsi et al. 2005). Stage T1–T2 N0 triple negative breast cancer has also been associated with a higher risk of locoregional recurrence after modified radical mastectomy in some studies (Abdulkarim et al. 2011), and there are data from a Chinese randomized trial that suggest that triple negative patients may benefit from postmastectomy radiotherapy even if node negative (Wang et al. 2011). Further research in this area will be important to confirm these findings, as triple negative status is not currently considered an indication for postmastectomy radiotherapy in the absence of other adverse features such as nodal involvement. The 2014 analysis from the EBCTCG found that in patients who underwent axillary dissection and had no involved lymph nodes, only 1.4 % experienced a locoregional recurrence, and radiotherapy did not appear to provide an appreciable benefit. However, few patients with T3 N0 disease were included, and this analysis did not include primary tumor size as a covariate; therefore, these data cannot be taken as evidence against offering radiotherapy to patients with a large primary tumor (McGale et al. 2014). Thus, although some patients with large tumors who are treated with mastectomy might not require radiation, consultation with a radiation oncologist is warranted to individually assess the risk of local recurrence.

Given the morbidity of a chest wall recurrence and low likelihood of successful salvage, it is interesting to observe the heterogeneity of data regarding the role of radiation in the setting of a positive margin after mastectomy. The incidence of chest wall recurrence has been reported as high as 18 % after 8 years in patients with a positive or close margin <5 mm (Freedman et al. 1998). However, in a cohort from British Columbia with positive margins, there were no recurrences observed in patients with age >50 years, T1 tumors, grade 1/2 disease, and absence of lymphovascular invasion, suggesting that not all patients with node-negative breast cancer with positive margins after mastectomy routinely require radiotherapy (Truong et al. 2004). A retrospective study from Harvard observed a significantly higher rate of locoregional recurrence with positive margins (6.2 %) compared to close margins (1.5 %), which was similar to the rate observed in patients with negative margins (1.9 %) (Childs et al. 2012). Collectively, these results suggest that while many patients with close or positive margins may derive significant benefit from postmastectomy radiation, particularly young patients, other subgroups are likely to derive a much smaller absolute benefit.

Determining the indications for postmastectomy radiation following neoadjuvant chemotherapy is an area of ongoing research. Patient selection for postmastectomy radiation has been based on pathologic features observed prior to exposure to systemic therapy in all of the previously published trials, and less is known regarding the role of radiation when the observed pathology reflects the response to systemic therapy. Retrospective studies suggest that both the initial clinical stage and the final pathologic extent of disease provide important prognostic information. Data from MD Anderson Cancer Center found that patients with clinical stage III disease who achieved a complete response to neoadjuvant chemotherapy still experienced a high rate of locoregional failure, which was significantly reduced with radiation (33 to 3 % at 10 years) (Huang et al. 2004). A follow-up study evaluating only patients who achieved a pathologic complete response to neoadjuvant chemotherapy confirmed these findings with clinical stage III disease, though patients with stage I or II disease who experienced a pathologic complete response did not experience locoregional recurrence with or without radiation (McGuire et al. 2007). In two NSABP trials of neoadjuvant chemotherapy, B18 and B27, none of the patients received postmastectomy radiation, allowing for evaluation of features associated with a high risk of locoregional recurrence in the absence of radiation (Mamounas et al. 2012). On multivariate analysis, clinical tumor size >5 cm, clinically positive lymph nodes, and less than a complete response in the breast and/or axillary lymph nodes were independent predictors of locoregional relapse. The risk of locoregional relapse was consistently >10 % for all subgroups of

patients with one to three residual positive lymph nodes after chemotherapy. Taken together, these results are reflected in a statement from a multidisciplinary expert panel organized by the National Cancer Institute, which recommended that chest wall and regional nodal radiation should be considered after mastectomy for patients who present with clinical stage III disease or have positive lymph nodes after preoperative chemotherapy (Buchholz et al. 2008). The role of postmastectomy radiation in patients with stage II breast cancer who have negative lymph nodes after chemotherapy remains an area of controversy. The indications for postmastectomy radiation after neoadjuvant chemotherapy will become clearer with results from the ongoing NSABP B-51/RTOG 1304 trial, in which patients who receive mastectomy and have a pathologic complete response in the axillary lymph nodes are randomized to postmastectomy radiation or no radiation.

In summary, there is strong consensus regarding the role of postmastectomy radiation in patients with ≥4 involved lymph nodes. Decisions regarding radiation for patients with one to three involved lymph nodes have previously been an area of controversy, though consensus is growing that postmastectomy radiation affords important benefits to this subgroup as well (McGale et al. 2014; Marks et al. 2008). Data are less conclusive on the role of postmastectomy radiation with positive margins, large or high-risk node-negative tumors (such as triple negative breast cancer), and following neoadjuvant chemotherapy. Regardless, all patients with locally advanced breast cancer who undergo mastectomy merit referral to a radiation oncologist to discuss the available data to facilitate individualized decision-making.

4.2 Management of the Regional Lymph Nodes

The rationale for radiation therapy to the regional lymph nodes is similar to that articulated for postmastectomy radiation therapy. Some patients may harbor disease in the regional nodal basins, regardless of whether their primary surgery was a mastectomy or a lumpectomy. Recurrence in these nodal regions is a morbid event worthy of prevention in patients at sufficient risk. Moreover, in select patients with lymph node involvement, the regional lymph node basins may be the only reservoir of residual disease after local surgery and systemic therapy, and therefore eradicating this disease may have an impact on overall survival as well as locoregional control. The Danish and Canadian postmastectomy trials included treatment to the supraclavicular, axillary, and internal mammary lymph nodes; some have extrapolated from those trials that radiation therapy to those regions also should be considered for patients with node-positive disease who undergo breast-conserving surgery.

In the National Cancer Institute of Canada MA-20 trial, after undergoing breast-conserving surgery and axillary lymph node dissection, patients with node-positive and high-risk node-negative breast cancer were treated with whole breast irradiation and randomly assigned to the addition of regional nodal irradiation that included the supraclavicular, internal mammary, and level III axillary lymph nodes. Of the patients enrolled, 85 % had one to three involved nodes (identified on axillary lymph node dissection rather than sentinel lymph node biopsy); 25 % were ER negative and 42 % were grade 3. Preliminary results demonstrated that the addition of regional nodal irradiation improves disease-free survival with a trend toward improved overall survival, with a reduction in distant metastasis (absolute risk reduction 5.4 %) that was greater than the reduction in regional recurrence rates (absolute risk reduction 2.3 %). Regional nodal radiation was well-tolerated, but associated with a higher risk of pneumonitis (1.3 % vs 0.2 %) and lymphedema (7.3 % vs 4.1 %) compared to whole breast irradiation alone (Whelan et al. 2011).

Similar findings were observed in the EORTC 22922/10925 trial, in which patients with involved axillary lymph nodes or a medial tumor were randomized to the addition of medial supraclavicular and internal mammary nodal radiation. In contrast to previous trials that have sought to determine the benefit of internal mammary nodal

radiation (Hennequin et al. 2013), the EORTC trial was adequately powered to detect a small survival benefit and randomized over 4000 patients. Preliminary results demonstrated significantly improved disease-free survival, metastasis-free survival, and a trend toward improved overall survival, which was independent of the number of involved lymph nodes. There was no appreciable increase in non-breast cancer mortality related to treatment toxicity (Poortmans et al. 2013). These preliminary results, when taken together with reported findings from MA-20, are suggestive of a survival benefit with regional nodal radiation, even in patients with one to three involved nodes, similar to findings in the postmastectomy setting (McGale et al. 2014). Additionally, because 44 % of patients enrolled on EORTC 22922/10925 had negative lymph nodes and a medially located tumor, regional nodal radiation is an important consideration for this subgroup as well.

The decision to treat with a supraclavicular field in patients with node-positive disease has generally been less controversial, given that a non-trivial minority of failures occur in this region (Taghian et al. 2004a; Wallgren et al. 2003; Katz et al. 2000; Grills et al. 2003) and that treatment results in little increase in the risks of pneumonitis, brachial plexopathy, and lymphedema. In contrast, considerable controversy surrounds the decision to treat the internal mammary lymph nodes, resulting in widespread variation in practice patterns (Taghian et al. 2004b; Clavel et al. 2010).

In historical series, patients with advanced primary disease and positive axillary lymph nodes had rates of pathologically confirmed IMN involvement of 28–52 % and up to 65 % when the tumor was centrally or medially located (Chen et al. 2008; Freedman et al. 2000). More recent data from patients with early breast cancer demonstrated primary internal mammary lymph node drainage on lymphoscintigraphy in 13–37 % of cases (Chen et al. 2008; Paredes et al. 2005; Farrus et al. 2004), which has been associated with a higher incidence of distant metastasis and risk of mortality (Yao et al. 2007; Kong et al. 2012). Furthermore, patients with a centrally or medially located tumor also have a higher risk of metastasis and lower survival (Zucali et al. 1998; Brautigam et al. 2009). Taken together, these results suggest that internal mammary nodal involvement is neither infrequent nor trivial and may serve as an occult reservoir that seeds distant metastases and significantly influences prognosis.

Interest in treating the internal mammary lymph nodes increased with publication of favorable results from the Canadian and Danish trials of postmastectomy radiation (Overgaard et al. 1997; Overgaard et al. 1999; Ragaz et al. 2005), which included treatment of the internal mammary lymph nodes. However, several clinical trials have failed to demonstrate an improvement in survival with internal mammary nodal radiation (Hennequin et al. 2013; Freedman et al. 2000), and older meta-analyses suggested that any benefit of internal mammary nodal radiation may be effaced by increased non-breast cancer mortality, largely related to increased cardiac-related deaths (Early Breast Cancer Trialists' Collaborative Group 1995; Cuzick et al. 1994; Palmer and Ribeiro 1985). However, computed tomography planning and strict quality assurance have been lacking in these studies (Buchholz 2000), and the increased mortality has been attributed to antiquated radiotherapy techniques that delivered significant dose to the heart and coronary vasculature. A follow-up of the Danish 82b and 82c trials of postmastectomy radiation, which included treatment of the internal mammary nodal regions using an electron field, demonstrated no increase in rates of morbidity and death from ischemic heart disease in patients who received internal mammary radiation (Hojris et al. 1999). More recently, an elegant population-based cohort study of internal mammary nodal irradiation, the Danish Breast Cancer Cooperative Group IMN study (DBCG-IMN), included internal mammary nodal radiation only in patients with right-sided breast cancer but not for left-sided tumors. Preliminary results revealed 3 % improvement in overall survival in patients who received internal mammary nodal radiation (Thorsen et al. 2013), which was felt to outweigh the risk of ischemic heart death even for left-sided tumors (Thorsen et al. 2014). The value of radiotherapy to the internal mammary lymph

nodes is further confirmed by preliminary results from MA-20 and EORTC 22922/10925, which, although unable to isolate the impact of supraclavicular versus internal mammary nodal irradiation, have thus far demonstrated improved distant disease-free survival without an increase in non-breast cancer mortality (Whelan et al. 2011; Poortmans et al. 2013).

The greatest controversy surrounds internal mammary nodal irradiation for patients with T1–T2 tumors and one to three involved positive axillary lymph nodes (Buchholz 2000). It is our practice not to advocate for internal mammary nodal treatment in cases in which the risk of involvement is low (e.g., micrometastatic axillary involvement), but rather when axillary involvement is more substantial, particularly when the tumor is medially located and other high-risk features exist. With modern radiotherapy techniques and respiratory gating, we have been able to cover internal mammary lymph nodes when indicated, while exposing the heart and coronary vasculature to only low-dose scatter (Jagsi and Pierce 2013; Chung et al. 2013), as discussed in greater detail in the section on cardiac toxicity below.

Concerns about the risk of lymphedema associated with directed axillary radiotherapy after axillary dissection have generally dissuaded physicians from directed axillary radiotherapy unless exceptional circumstances exist, such as concerns about residual disease in the setting of extensive nodal disease, gross extranodal extension, or incomplete dissection. However, as a result of findings from two randomized trials – the American College of Surgeons Oncology Group Z0011 trial (Giuliano et al. 2010, 2011) and the International Breast Cancer Study Group 23-01 trial (Galimberti et al. 2013) – complete dissection of axillary levels I and II is no longer routine for patients with limited sentinel node involvement. The Z0011 trial randomized patients who had clinical T1–T2 invasive breast cancer, no palpable adenopathy, and one to two involved sentinel lymph nodes to axillary lymph node dissection versus no further axillary surgery. After 6.3 years of follow-up, local-regional recurrence rates and overall survival were equivalent between the two arms. Similar findings were observed in the IBCSG trial. Both trials demonstrated a rate of disease recurrence in the undissected axilla <1 %, suggesting that axillary dissection can be avoided in patients with early breast cancer and limited sentinel node involvement similar to those treated on these two trials.

The results of Z0011 and IBCSG 23-01 have quickly assimilated into routine clinical practice (Gainer et al. 2012; Massimino et al. 2012; Caudle et al. 2012), resulting in decreased use of axillary lymph node dissection. It is therefore not uncommon for a patient with positive sentinel lymph node to forego axillary lymph node dissection, even for patients who would not have been eligible for inclusion in Z0011 and IBCSG 23-01 or who have disease features that were uncommonly represented in the patients enrolled on those trials. For example, many breast surgeons are willing to consider omission of axillary lymph node dissection even in patients who will be treated with accelerated partial breast irradiation or who are not planning to receive radiation, despite the lack of data to support axillary lymph node dissection omission in this scenario (Gainer et al. 2012). Furthermore, some consider that the results of these two trials are applicable to all patients who would technically have been eligible for the studies, while others argue that the results are most applicable to patients who resemble the majority of patients who enrolled. For example, in both trials, 69–70 % had T1 tumors, 82–90 % had estrogen receptor-positive disease, and 71–96 % had only one positive sentinel lymph node. In Z0011, 41 % had micrometastatic nodal disease, in contrast to 98 % in IBCSG 23-01, which excluded patients with nodal macrometastatic disease. While premenopausal patients with a T2 tumor, hormone receptor-negative disease, and macrometastasis technically might have been eligible for one or both of these trials, the results of the trials may not be generalizable to patients lacking the favorable disease features that characterized the majority of patients who were actually enrolled.

Particularly challenging has been reconciling the results of NCIC MA20 and EORTC 22922, which seem to suggest a benefit with extensive nodal treatment including radiation of the

supraclavicular and internal mammary regions, with those of ACOSOG Z0011 and IBSCG 23-01, which suggest that perhaps even completion dissection is unnecessary, let alone regional irradiation. All of these trials primarily enrolled patients with N1 disease, though those in the former studies were likely higher-risk N1 patients than those in the latter. In any case, considerable controversy surrounds the optimal radiation field design in patients with limited disease detected on sentinel node biopsy, who have not received axillary lymph node dissection. Although the Z0011 study protocol required standard tangential radiotherapy, 51 % of evaluable patients were actually treated with high tangents and 19 % received directed regional nodal radiation using three or more fields (Jagsi et al. 2014c). While there was notably no difference between the arms in the use of protocol-prohibited nodal fields, the use of directed nodal irradiation in some patients has led to the conclusion that it is not unreasonable also to consider additional nodal treatment in selected patients who receive sentinel node biopsy alone for limited nodal disease.

Further insights have recently emerged from the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) trial, which randomized patients to completion axillary lymph node dissection or radiation to regional lymph nodes. The AMAROS protocol specified that the radiation field included the medial supraclavicular and level I–III axillary lymph nodes (with coverage of the internal mammary lymph nodes in 10 %, at the discretion of the treating physician). Disease characteristics on AMAROS were similar to Z0011: 80 % had T1 tumors, 77 % had one involved node, and 40 % had nodal micrometastasis or isolated tumor cells. Patients who received axillary radiotherapy had significantly less lymphadenopathy and postoperative complications in comparison to those who underwent axillary lymph node dissection, with comparable axillary control, suggesting that axillary radiotherapy may be preferred over axillary lymph node dissection in patients with a positive sentinel lymph node (Donker et al. 2014).

Thus, in patients with involved sentinel node(s) who forego axillary lymph node dissection, there is a spectrum of appropriate radiotherapy treatment fields ranging from conventional tangential fields to comprehensive breast and regional nodal irradiation. Intentionally targeting the axilla with high tangents can be accomplished with minimal adjustments to tangent field borders (Schlembach et al. 2001; Shahar et al. 2004). Nomograms may be helpful in determining the risk of having additional involved nodes in the undissected axilla and the need for a third field (Haffty et al. 2011; Center MSKC Breast Cancer Nomogram: Breast Additional Non SLN Metastases; Center MAC Breast Cancer Nomogram to Predict Additional Positive Non-SLN, without Neoadjuvant Chemotherapy).

Ultimately, all patients with macrometastatic involvement of the regional nodes, regardless of whether their primary tumor was treated with lumpectomy or mastectomy, are candidates for consideration of directed regional nodal radiotherapy. Decision-making must take into account multiple risk factors, including the extent of the nodal involvement, the axillary surgical procedure performed, the biology of the tumor, and systemic therapy receipt. It must also consider the patient's preferences with regard to prevention of recurrence versus avoidance of possible treatment-related toxicities, so that the treatment plan is appropriately individualized for each patient.

4.3 Cardiac Toxicity Associated with Breast Radiotherapy

Due to the proximity of the left ventricle and left anterior descending coronary artery to the chest wall and internal mammary lymph nodes, radiotherapy may result in significant dose to cardiac structures, causing increased cardiac toxicity. This likely accounts for the observation in the early EBCTCG meta-analyses (Early Breast Cancer Trialists' Collaborative Group 1995; Early Breast Cancer Trialists' Collaborative Group 2000) of improved breast cancer-specific survival with radiation, which was offset by increased risk of death from other causes, notably from vascular-related mortality. While several

individual studies did not find an increased risk of cardiac events or death from a cardiac cause associated with radiation (Hojris et al. 1999; Gustavsson et al. 1999; Rutqvist et al. 1998), larger population-based analyses (Paszat et al. 1998) and single institution series (Jagsi et al. 2007a; Harris et al. 2006) observed increased risk of cardiac events and cardiac mortality with left-sided breast cancer in comparison to patients with a right-sided tumor. A Swedish group described a positive correlation between death due to cardiovascular disease and irradiated cardiac dose and volume (Gyenes et al. 1998). A recent landmark population-based study from Denmark and Sweden found that there was a proportional increase in ischemic heart disease with increasing mean dose to the heart (7.4 % relative increase per 1 gray), with no apparent threshold below which no risk was incurred (Darby et al. 2013b). However, the radiation doses to the heart in this study were estimated by virtually reconstructing each patient's radiation plan "on the CT of a woman with typical anatomy" and may be least accurate in the low-dose region (<4 Gy), which is most relevant to current practice. Nonetheless, the study highlights the importance of minimizing the radiation dose to the heart.

The risk of death from ischemic heart disease after breast radiotherapy has decreased substantially over time (Giordano et al. 2005) with development of more sophisticated treatment planning techniques and increased awareness of minimizing radiation dose to the heart. In a population-based evaluation of 10,468 patients with ductal carcinoma in situ who were treated between 1989 and 2004, after median follow-up of 10 years, there was no evidence of increased risk for cardiovascular morbidity or mortality after radiotherapy when compared to surgery alone, nor when comparing radiotherapy for left-sided versus right-sided DCIS (Boekel et al. 2014; Feng and Pierce 2014).

However, it is concerning to note that radiation dose to the heart has been associated with cardiac perfusion defects. In a prospective study that evaluated pre- and posttreatment cardiac perfusion imaging, radiation caused volume-dependent perfusion defects in approximately 40 % of patients within 2 years of radiation, which were associated with corresponding wall motion abnormalities (Marks et al. 2005). However, although this study used CT-based treatment planning, it allowed inclusion of anterior portions of the heart within the tangential fields, and there was significantly increased incidence of perfusion defects with a greater volume of left ventricle within the radiation field. Furthermore, the clinical consequences of these abnormalities have not been defined, and there has been no associated change in ejection fraction. Reassuringly, in a similar prospective study in which no portion of the heart was allowed within the primary beam, there were no detectable perfusion defects 1 year after radiation (Chung et al. 2013).

Collectively, these studies clearly establish a relationship between radiation exposure to the heart and cardiac toxicity. However, it is important to note that the net overall survival benefit of radiation in the trials above and with longer follow-up of the EBCTCG meta-analyses (Clarke et al. 2005; Darby et al. 2011a; McGale et al. 2014) already account for any adverse effect from radiation-related cardiac toxicity. Therefore, patients who are likely to obtain significant benefit from radiation should not forego treatment due to concerns related to cardiac exposure. Current guidelines recommend that the heart should be excluded from the primary treatment fields (Smith et al. 2011c). This becomes feasible with CT-based treatment planning and respiratory motion management, such as deep inspiratory breath hold (Remouchamps et al. 2003; Jagsi et al. 2007b) or respiratory gating. With increased awareness regarding the importance of cardiac dose, the risks associated with breast radiotherapy will be further minimized with careful treatment planning and modern treatment techniques.

Conclusion

Considerable progress is being made toward appropriately selecting patients most likely to benefit from radiation, defining treatment targets, and reducing the burden and morbidity associated with treatment. At the present time, decisions regarding radiation are largely

informed by clinical and pathological features. Efforts to identify a subgroup of patients at sufficiently low risk of recurrence to forego radiotherapy suggest that clinical and pathologic features provide insufficient discriminatory power. There is an increasing appreciation of the influence of tumor biology on the risk of local and distant recurrence (Mamounas et al. 2010; Cheng et al. 2006; Nguyen et al. 2008; Millar et al. 2009; Voduc et al. 2010), as well as response to treatment (Abdulkarim et al. 2011; Paik et al. 2006; Kyndi et al. 2008). These findings highlight the central importance of obtaining a more comprehensive understanding of tumor biology and lend support to ongoing efforts to refine the accuracy of genomic assays with prognostic and predictive significance. Ultimately, a more thorough understanding of tumor biology will facilitate individualized treatment decisions, with sparing of those with low-risk disease from unnecessary treatment, targeting those most likely to benefit, and intensifying treatment for those likely to recur with currently available therapies.

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Center MAC Breast Cancer Nomogram to Predict Additional Positive Non-SLN, without Neoadjuvant Chemotherapy

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Lung Cancer and Other Thoracic Malignancies

Matthew M. Harkenrider, Scott R. Silva, and Roy H. Decker

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Abstract

Lung cancer is the deadliest malignancy in the United States, and much research has been dedicated over the last many decades to improve patient outcomes. Smoking cessation education, lung cancer screening, improved diagnostic and functional imaging, improved surgical and radiation techniques, multimodality therapy, and targeted biologic and immunologic therapy have all lead to earlier detection of lung cancer and improved treatment resulting in improvements in overall survival. There are still many controversies that exist within each of these many aspects in the diagnosis and treatment of lung cancer. This chapter is dedicated to the controversies that exist in the management and treatment of all aspects of lung cancer with additional discussion of the controversies regarding thymoma and malignant pleural mesothelioma.

1 Lung Cancer

Lung cancer is the second most common malignancy and the leading cause of cancer death in the United States. Lung cancer is primarily related to cigarette and other types of tobacco smoking, though secondhand smoke exposure, radon, and environmental exposures also contribute to lung cancer incidence. Fortunately, the rates of new lung cancer diagnoses and lung cancer-related deaths are decreasing as smoking has become less prevalent (A Snapshot of Lung Cancer).

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Historically, early-stage lung cancer has been treated surgically and advanced disease with concurrent radiochemotherapy. In this section, the evolution and controversies of lung cancer treatment are discussed with the emphasis on those pertaining to radiotherapy.

1.1 Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) comprises 85–90% of lung cancer with adenocarcinoma and squamous cell carcinoma being the most common. The majority (~55%) of patients have metastatic disease at diagnosis and the 5-year survival of all patients with newly diagnosed NSCLC is only 17% (SEER Cancer Statistics Factsheets: Lung and Bronchus Cancer). Due to the high incidence and poor survival, there has been significant interest in screening for lung cancer. The National Lung Screening Trial evaluated patients at high risk for lung cancer (age 55–74 and ≥30 pack-year smoking history) with annual low-dose computed tomography (CT). A 20% reduction in lung cancer mortality was demonstrated with low-dose CT screening (National Lung Screening Trial Research Team et al. 2011). With lung cancer screening, earlier-stage disease and potentially curable patients can be treated prior to development of metastases. In this section, the controversies regarding the management of NSCLC will be reviewed with an emphasis on the role of radiotherapy.

1.1.1 Early-Stage NSCLC

Surgery

Early-stage NSCLC will become an increasing portion of the radiation oncologist's patient population as more institutions establish lung cancer screening programs. Early-stage NSCLC is classically treated surgically with lobectomy with hilar and mediastinal lymph node dissection. Martini et al. reported surgical results with an approximately 95% locoregional control rate with 5- and 10-year overall survival of 75% and 67%, respectively (Martini et al. 1995). However, a lobectomy can result in inferior pulmonary function preservation, and many patients with poor cardiopulmonary function will not tolerate lobectomy. Sublobar resections with either segmentectomy or wedge resections can be considered for patients with suboptimal lung function. The Lung Cancer Study Group trial investigated lobectomy vs. sublobar resection for T1 N0 NSCLC and demonstrated an improved local recurrence rate with lobectomy (6%) compared with sublobar resection (17%; $p = 0.02$) (Ginsberg and Rubinstein 1995). Furthermore, the severity of the patient's comorbidities may preclude any surgical intervention including lung-sparing surgeries such as wedge resection.

External Beam Radiotherapy

Historically, medically inoperable early-stage NSCLC patients were offered definitive external beam radiotherapy (EBRT) as primary management, but studies showed poor rates of local control (Qiao et al. 2003; Dosoretz et al. 1992; Sibley et al. 1998; Zierhut et al. 2001). Qiao et al. reviewed 18 studies of stage I NSCLC treated with EBRT alone and showed a median local recurrence rate of 40% with 5-year overall survival rate of 21% (Qiao et al. 2003). Trends of improved local control and lower intrathoracic recurrence rates were reported with increasing radiation dose, providing a rationale for dose escalation (Qiao et al. 2003; Kaskowitz et al. 1993; Kupelian et al. 1996). Although studies using dose escalation with conventionally fractionated EBRT have shown improved outcomes, the results remained far inferior to surgical intervention (Chen et al. 2006; Kong et al. 2006).

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is a technique which delivers very high doses of radiation per fraction over a few number of fractions to precisely defined volumes with steep dose gradients. Patient immobilization, setup reproducibility, image guidance, and tumor motion management are critical to ensure target coverage and normal tissue sparing. SBRT was first studied for the treatment of biopsy-proven early-stage NSCLC in medically inoperable patients. An increasing amount of evidence demonstrates the

feasibility, safety, and efficacy of SBRT in this patient population (Onishi et al. 2004; Nagata et al. 2005; Fakiris et al. 2009; Lagerwaard et al. 2012). Local control rates of 80–98% have been consistently reported (Onishi et al. 2004; Nagata et al. 2005; Fakiris et al. 2009; Lagerwaard et al. 2012; Uematsu et al. 2001; Baumann et al. 2009; Timmerman et al. 2010; Timmerman et al. 2014; Ricardi et al. 2010; Verstegen et al. 2011; Bral et al. 2011; Takeda et al. 2012). Yet heterogeneous dose schedules, total dose, and dose delivery methods in these institutional studies make it difficult to standardize SBRT.

In the early work from Indiana University, Timmerman et al. treated 70 patients with early-stage (T1–T2), inoperable NSCLC with 60 Gy in three fractions for T1 tumors and 66 Gy in three fractions for T2 tumors. Primary tumor control was 95% at 2 years. With a median follow-up of 17.5 months, grade 3–5 adverse events occurred in 14 out of the 70 patients (20%) with six treatment-related deaths. Central tumor location, defined as tumors within 2 cm of the proximal bronchial tree, was a significant factor related to adverse event occurrence; freedom from severe toxicity at 2 years was 83% for peripheral lung tumors compared to 54% for central lung tumors (Timmerman et al. 2006). With longer follow-up, the 3-year local control was 88.1%, and 3-year overall survival and cancer-specific survival were 42.7% and 81.7%, respectively. The rate of grade 3–5 toxicity remained significantly higher for central lesions (27%) compared to peripheral lesions (10%) (Fakiris et al. 2009). These results established that central tumors should be approached differently than peripheral tumors. Radiation Therapy Oncology Group (RTOG) 0236 study, the first major multi-institutional Phase II SBRT study, delivered SBRT (54 Gy in three fractions) to medically inoperable patients with biopsy-proven peripheral early-stage (<5 cm) NSCLC. For the 55 evaluable patients, 3- and 5-year local control rate was 97.6% and 93.0%, respectively, and 3- and 5-year overall survival was 55.8% and 40%, respectively. Grade 3 and 4 adverse events occurred in seven patients (12.7%) and two patients (3.6%) at 3 years and 15 patients (27.3%) and two patients (3.6%) at 5 years, respectively (Timmerman et al. 2010, 2014). Though these studies used a three-fraction SBRT schedule, there are many dose-fractionation regimens that have been reported with comparable outcomes as shown in Table 1.

Though numerous schedules may be used, one method of comparing different regimens is by calculating the biologic effective dose (BED) using the linear quadratic model. Onishi et al. published a multi-institutional retrospective series of 257 lung cancer patients treated with SBRT using several dosing schedules. Patients receiving a $BED_{(\alpha/\beta=10)}$ ≥100 Gy vs. <100 Gy endured fewer local recurrences (8.1% vs. 42.9%, $p < 0.001$) and experienced significantly improved 5-year overall survival (70.8% vs. 30.2%, $p < 0.05$) (Onishi et al. 2007). A population-based study showed that there was improved overall survival for a higher BED of >150 Gy for T2 tumors but no difference for T1 tumors (Koshy et al. 2015).

The results of the initial Indiana University study showed an unacceptable level of toxicity for patients treated with 60–66 Gy in three fractions (Timmerman et al. 2006). Controversy exists whether SBRT of any dose-fractionation schedules is safe for centrally located tumors. RTOG 0813 further investigated SBRT for central tumors with a Phase I/II dose-escalation/de-escalation study starting at 50 Gy in five fractions. The study successfully escalated doses to 60 Gy in five fractions with dose-limiting toxicity in 7.2% of patients among all dose levels (Bezjak et al. 2016). Centrally located lesions can safely be treated to doses of 48–60 Gy in 4–5 fractions or 60 Gy in eight fractions based on single-institution studies (Chang et al. 2008; Stephans et al. 2009; Haasbeek et al. 2011; Mangona et al. 2015; Bradley et al. 2015a). Dose-fractionation schedules and results of SBRT for centrally located tumors are shown in Table 2.

Some additional concerns for toxicity may influence fractionation schedules. Pneumonitis, pulmonary fibrosis, and obstructive pulmonary processes are the most commonly described toxicities. The symptomatic lung toxicity rate is reported as 9.2–20.3% (Barriger et al. 2012; Matsuo et al. 2012; Baker et al. 2013). Compared

Table 1 Dose-fractionation schedules and results of prospective SBRT trials

Author (year)	Type/stage	No. of patients	Dose	Median follow-up	Local control	Overall survival
Nagata et al. (2005)	Phase I–II/stage I NSCLC	45	12 Gy × 4	30 months	1-year LC: 100% 5-year LC: 98%	1-year OS: 80% 5-year OS: 70%
Fakiris et al. (2009)	Phase II/T1–2N0M0 NSCLC	70	20 Gy × 3 for T1 tumors (n = 34) 22 Gy × 3 for T2 tumors (n = 36)	50.2 months	3-year LC: 88.1%	3-year OS: 42.7%
Baumann et al. (2009)	Phase II/stage I NSCLC	57	15 Gy × 3 to 67% IDL	35 months	3-year LC: 92%	3-year OS: 60%
Timmerman et al. – RTOG 0236 (2010, 2014)	RTOG Phase II/ T1–2N0M0 NSCLC (peripherally located)	55	18 Gy × 3	34.4 months (2010) 48.0 months (2014)	3-year LC: 97.6% 5-year LC: 93.0%	3-year OS: 55.8% 5-year OS: 40.0%
Ricardi et al. (2010)	Phase II/stage I NSCLC	62	15 Gy × 3 to 80% IDL	28 months	3-year LC: 87.8%	3-year OS: 57.1%
Bral et al. (2011)	Phase II/T1–3N0M0	40	20 Gy × 3 (peripheral) 15 Gy × 4 (central)	16 months	2-year LPFS: 84%	2-year OS: 52%
Timmerman et al. – RTOG 0618 (2013)	Phase II/T1–3N0M0 (operable)	26	18 Gy × 3	25 months	2-year LC: 92.3%	2-year OS: 84.4%
Videtic et al. – RTOG 0915 (2015)	Phase II/T1–2N0M0	84	34 Gy × 1 (n = 39) vs. 12 Gy × 4 (n = 45)	30.2 months	1-year LC: 97.0% vs. 92.7%	2-year OS: 61.3% vs. 77.7%
Chang & Senan et al. – STARS/ROSEL (2015)	Phase III/T1–2aN0M0	31	18 Gy × 3 (peripheral) 12.5 Gy × 4 (central) 12 Gy × 5 (n = 5)	40.2 months	3-year LC: 96%	3-year OS: 95%
Nagata et al. (2015)	Phase II/T1N0M0	100 inoperable 64 operable	12 Gy × 4	47 months (inoperable) 67 months (operable)	Inoperable: 3-year LC: 87.3% Operable: 3-year LC: 85.4%	Inoperable: 3-year OS: 59.9% Operable: 3-year OS: 76.5%

Table 2 Dose-fractionation schedules and results of SBRT studies for centrally located tumors

Author (year)	Type/stage	No. of patients	Dose	Median follow-up	Local control	Overall survival	Acute toxicity	Late toxicity
Chang et al. (2008)	Retrospective/T1–2N0M0 or isolated lung recurrence	27	10 Gy × 4 (n = 7) 12.5 Gy × 4 (n = 20)	17 months	LC: 100% at 17 months for 50 Gy group; 57.1% for 40 Gy group	Not reported		Grade 2 pneumonitis: 14.8% (all recurrent disease) Grade 2–3 dermatitis and chest wall pain: 11.1%
Haasbeek et al. (2011)	Retrospective/T1–3N0M0	63	7.5 Gy × 8	35 months	3-year LC: 92.6%	3-year OS: 64.3%	Grade 2 dyspnea: 3.2% Grade 2–3 chest wall pain: 3.2%	Grade 2–3 dyspnea: 6.3% Grade 2–3 chest wall pain: 4.8%
Mangona et al. (2015)	Retrospective/T1–2N0M0 or isolated local recurrence or stage IV/non-lung primary	79	12 Gy × 4 (n = 45) 12 Gy × 5 (n = 30) 10 Gy × 5 (n = 3) 11 Gy × 5 (n = 1)	17.3 months	2-year LC: 91.4%	2-year OS: 71.7%	Grade 2 radiation dermatitis: 3.4% Grade 2 fatigue: 2.5%	Grade 2 chest wall pain: 6.9% Grade 2 myositis: 3.4% Grade 2 rib fracture: 5.2% Grade 2 soft tissue fibrosis: 3.4% Grade 2–3 fatigue: 6.9% Pneumonitis: 0%
Bradley et al. (2015a)	Prospective phase II/early stage	41	11 Gy × 5	11.9 months	1-year LC: 95.4%	1-year OS: 81.2%	Grade 3 hypoxia: 2.4%	Grade 3: 3/41 Grade 4 lung atelectasis and dyspnea: 4.9% Grade 5 fatal hemoptysis: 2.4%
Bezjak et al. (2016)	Phase I/T1–2N0M0	89	10 Gy × 5– 12 Gy × 5	26.6 months	Not reported	Not reported		Grade 3–4 bradycardia, hypoxia, or pneumonitis: 12.4% Grade 5: 4.5%

to the early three-fraction regimens, more protracted courses of SBRT appear to have similar rates of lung toxicity for central and peripheral lesions (Haasbeek et al. 2011; Mangona et al. 2015). As mentioned, doses such as 50–55 Gy in five fractions are most commonly delivered for central lesions (Daly et al. 2013). Lesions that are proximate to the esophagus can lead to rare high-grade esophageal toxicity (Stephans et al. 2014; Stang et al. 2015). With a three-fraction SBRT regimen, patients with apical lung tumors had a grade 2–4 brachial plexopathy rate of up to 20%. Those patients with maximum dose to the brachial plexus ≥26 Gy experienced a significantly greater rate of brachial plexopathy (Forquer et al. 2009). Higher doses to the chest wall and adjacent rib for peripheral tumors have also resulted in increased rates of chest wall pain and rib fracture (Dunlap et al. 2010). A scenario where the tumor abuts an organ at risk, even the chest wall, warrants consideration for a more prolonged, often 5–8 fraction, course of SBRT.

Peripheral tumors have also been treated with a variety of dose-fractionation schedules. RTOG 0915 is a randomized Phase II trial which compared two dose schedules for small peripheral lung tumors – 34 Gy in one fraction vs. 48 Gy in four fractions (Videtic et al. 2015). RTOG 0915 showed that adverse events were no different for 34 Gy in one fraction vs. 48 Gy in four fractions (10.3% vs. 13.3%, respectively). Primary tumor control at 1 year was also comparable at 97.0% and 92.7%, respectively. A three-fraction SBRT regimen of 54–60 Gy is still the most commonly used dose-fractionation schedule for peripheral early-stage NSCLC though (Daly et al. 2013).

As data have matured, SBRT has gained a reputation for being a safe, nonsurgical option for early-stage lung cancer. Even medically operable patients may prefer or may be advised by their physicians to consider a nonsurgical option with SBRT. RTOG 0618 was a study of SBRT for medically operable patients with early-stage NSCLC. They showed 2-year local control of the primary tumor of 92.3%, 2-year overall survival of 65.4%, and grade ≥3 adverse event rate of 16% (Timmerman et al. 2013). Additionally, Nagata et al. reported on their population of medically operable patients with 3-year local control of 85.4%, 3-year overall survival of 76.5%, and grade 3 toxicity rate of 7.8% (Nagata et al. 2015).

Several analyses of SBRT and various forms of surgical resection have been performed. Grills et al. showed that SBRT had superior local control when compared to wedge resection though operable patients had improved overall survival with no difference in cause-specific survival. SBRT patients had greater comorbidities than the operable patients as expected (Grills et al. 2010). Hamaji et al. reported a retrospective matched pair analysis comparing video-assisted thoracoscopic surgical (VATS) lobectomy to SBRT. They reported that all survival and local control endpoints were improved with VATS lobectomy though this study was small and the SBRT dose was low (48 Gy in four fractions prescribed to the isocenter) (Hamaji et al. 2015). A meta-analysis compared surgery and SBRT studies for stage I NSCLC and found no difference in survival when adjusted for operability and age (Zheng et al. 2014).

The aforementioned prospective and comparative studies led to great interest in comparing SBRT to surgery in Phase III, randomized trials. Three randomized trials of surgery vs. SBRT have been initiated but failed to accrue. Chang and Senan et al. reported the combined results of two similarly designed studies (STARS/ROSEL). These studies randomized patients with stage I NSCLC to SBRT or lobectomy with lymph node dissection. With total accrual (from both studies) of 58 patients, local control was no different between arms, but SBRT had improved 3-year overall survival of 95% vs. 79% compared to lobectomy ($p = 0.04$) (Chang et al. 2015). There were only seven total deaths in this population though, so drawing conclusions on survival, given the combined analysis of two trials that failed to accrue, should be done with caution. Additional randomized studies are under way which will hopefully fully accrue and provide more conclusive data on this debate between surgery and SBRT for operable early-stage NSCLC patients (Moghanaki and Chang 2016).

The aforementioned major studies required histologically proven NSCLC. A subset of

patients present with clinical and radiographic evidence highly suspicious for malignancy, but pathological diagnosis cannot be obtained. The reasons for lack of tissue diagnosis may include comorbid conditions making biopsy too risky, tumor location that is not amenable to biopsy, patient refusal, biopsy was attempted but was nondiagnostic, or a biopsy-related complication occurred. In the absence of pathological diagnosis, clinical history, serial computed tomography (CT) scans, and 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) scans are capable of identifying lesions with high probability of malignancy. A meta-analysis on the accuracy of FDG-PET for detecting malignancy in solitary pulmonary lesions reported a mean sensitivity of 93.9% and mean specificity of 85.8% (Gould et al. 2001). In regions with endemic infectious granulomatous disease, PET retains its high sensitivity (92%) and positive predictive value (86%) with lower specificity (40%) (Deppen et al. 2011). Imaging findings on CT such as spiculation, ragged borders, pleural retraction, and nodule size (>1.5 cm) can be highly suggestive of malignancy. Harders et al. demonstrated the diagnosis of malignancy (vs. benignity) was five times more likely for nodules with spiculated or ragged margins and two times more likely in the presence of pleural retraction (Harders et al. 2011). In the presence of multiple CT scans, detection of growth strongly suggests malignancy (Gould et al. 2013). A validated clinical prediction model from the Mayo Clinic identified older age, current or past smoking history, and history of extrathoracic cancer as independent clinical predictors of malignancy (Swensen et al. 1997). Overall, clinical factors combined with radiographic findings can be highly predictive of malignancy, and validated clinical prediction models exist to quantify the overall probability of malignancy (Chang et al. 2008; Stephans et al. 2009). In patients where biopsy is contraindicated, these resources can guide treatment decisions. A recent decision analysis showed that the delivery of SBRT without a pathological diagnosis is justified if the likelihood of malignancy is ≥85% (Louie et al. 2014).

Currently, outcomes reported in the literature regarding the unbiopsied NSCLC patient population are limited. A retrospective analysis by Verstegen et al. included 591 stage I NSCLC patients undergoing SBRT, and 382 of these patients did not undergo biopsy prior to treatment. SBRT dose was 60 Gy in three, five, or eight fractions over 2 weeks. There were no differences in overall survival or local control rate in patients with or without pathological diagnosis (Verstegen et al. 2011). Retrospectively reporting on the Japanese population, Takeda et al. compared 58 clinically diagnosed lung cancer patients to 115 pathologically diagnosed NSCLC patients. All patients were treated with 40–50 Gy in five fractions. No significant difference for the two groups existed for 3-year local control (80% vs. 87%), regional failure-free survival (88% vs. 91%), metastasis-free survival (70% vs. 74%), progression-free survival (64% vs. 67%), cause-specific survival (74% vs. 71%), and overall survival (54% vs. 57%) rates (Takeda et al. 2012). Unlike patients in the Midwest and Southeast United States, the Dutch and Japanese populations have a very low incidence of benign granulomatous disease. A multi-institutional retrospective study by Harkenrider et al. analyzed SBRT in 34 non-pathologically diagnosed early-stage NSCLC patients from regions of endemic granulomatous disease. At a median follow-up of 16.7 months, local control was 97%, and the estimated 2-year overall survival was 85%. No acute grade ≥3 toxicities occurred, and three patients experienced late grade 3 dyspnea (8.8%) (Harkenrider et al. 2014). Recent SBRT prospective trials have incorporated unbiopsied NSCLC patients, but these studies are not from the United States (Baumann et al. 2009; Ricardi et al. 2010).

Brachytherapy

For patients undergoing surgical resection, lobectomy with lymph node dissection remains the standard of care. Since sublobar resection can result in increased rates of local failure, intraoperative brachytherapy has been studied with the goal of decreasing local recurrence rates. A pilot study from the University of Pittsburgh showed that (I-125) intraoperative brachytherapy is well

tolerated without decline in pulmonary function testing (Chen et al. 1999). They also reported their long-term series of 145 patients with a median follow-up of 38 months. They demonstrated a local failure rate of only 4.1%, and the treatment remained well tolerated (Colonias et al. 2011). They additionally compared their series of patients treated for early-stage NSCLC with sublobar resection with I-125 mesh brachytherapy to those treated with sublobar resection alone. With over 100 patients in each group, they showed that the local failure rate decreased from 18.6% to 2.0% with the addition of I-125 mesh brachytherapy (Santos et al. 2003). Birdas et al. evaluated the role of sublobar resection with brachytherapy vs. lobectomy and found local recurrence rates to be 4.8% and 3.2% ($p = 0.60$), respectively, with equivalent disease-free survival at 4 years (Birdas et al. 2006). These institutional experiences indicate that sublobar resection with brachytherapy is safe and feasible. Additionally, cancer-specific outcomes treated with sublobar resection appear to be improved with the addition of brachytherapy, and for high-risk patients, brachytherapy may be a good alternative to lobectomy.

These favorable results were subsequently tested by the American College of Surgeons Oncology Group (ACOSOG) Z4032 trial, a Phase III randomized study of high surgical risk patients with early-stage NSCLC. Patients were randomized to sublobar resection ± intraoperative brachytherapy. They found no difference in 5-year local relapse, 14.0% and 16.7% ($p = 0.59$) without and with brachytherapy, respectively. This study was powered to detect a large difference in local recurrence, so a potentially small but meaningful difference could not be detected (Fernando et al. 2014). Additionally, the local recurrence rate was lower with sublobar resection alone compared to the previous Lung Cancer Study Group trial which may be a result of increased surgeon attention to obtaining a negative surgical margin (Ginsberg and Rubinstein 1995).

The role of brachytherapy following sublobar surgical resection of early-stage NSCLC remains controversial especially given the conflicting data from ACOSOG Z4032.

1.1.2 Locally Advanced NSCLC

Stage III NSCLC is routinely treated with multimodality therapy, most commonly with concurrent radiochemotherapy (ChemoRT) for unresectable N2 and N3 disease. Surgery may be considered following neoadjuvant ChemoRT or chemotherapy alone for medically operable patients with favorable, low-volume N2 disease. Postoperative radiation therapy (PORT) may be considered for patients with positive margins or incidental mediastinal nodal involvement following surgery, though, historically, there has been much debate regarding the utility of PORT for NSCLC. In this section, the many issues and controversies regarding the management of locally advanced NSCLC will be discussed.

Definitive Radiochemotherapy

One of the earliest clinical trials within the RTOG addressed the appropriate dose for locally advanced NSCLC patients. RTOG 7301 demonstrated improved rates of intrathoracic recurrence with 60 Gy compared to 50 Gy, 40 Gy, or 40 Gy split course (Perez et al. 1980). Since then, groups have studied dose escalation with radiation therapy alone or with concurrent chemotherapy. In studies of radiation therapy alone, doses above 90 Gy were too toxic in RTOG 9311, while data from University of Michigan indicated that dose escalation improved survival (Bradley et al. 2005a; Wang et al. 2009).

The addition of chemotherapy to radiation therapy sequentially improved survival and decreased rates of distant metastases for locally advanced NSCLC (Komaki et al. 1997; Sause et al. 2000). RTOG 9410 subsequently demonstrated improved survival with concurrent ChemoRT over sequential therapy and established standard fractionation radiation therapy with concurrent platinum-based doublet chemotherapy as the standard of care. Even with these advances, median survival was still only 17 months (Curran et al. 2011). It was hoped that combining escalated doses of radiotherapy with concurrent chemotherapy would further improve patient survival. RTOG 0117 was a Phase I/II study of dose escalation to 74 Gy with concurrent chemotherapy and showed median survival of 21

months for stage III NSCLC patients (Bradley et al. 2010). Similarly, the Cancer and Leukemia Group B (CALGB) 30105 study demonstrated median survival of 24 months with 74 Gy and concurrent chemotherapy (Socinski et al. 2008).

These studies lead to RTOG 0617, a Phase III randomized study of concurrent ChemoRT with two randomizations – (1) 60 Gy vs. 74 Gy and (2) with vs. without cetuximab. Disappointingly, both randomizations yielded negative results. There was no difference in survival with the addition of cetuximab. Dose escalation to 74 Gy surprisingly resulted in significantly inferior survival compared to 60 Gy. The median survival was 28 months and 20 months for patients receiving 60 Gy and 74 Gy, respectively. There are several potential contributing factors to the inferior survival with dose escalation. There were more treatment-related deaths on the dose-escalation arm. Dose escalation was associated with inferior completion of chemotherapy, inferior target volume coverage, and increased heart dose. When only radiation plans that complied with target volume coverage were analyzed, dose escalation still had inferior survival, so poor target coverage does not explain the inferior survival. Cardiac toxicity and deaths were not specifically tracked on the study, but both V5 and V30 (percentage of the organ receiving 5 Gy and 30 Gy, respectively) of the heart predicted for patient death, so it is possible that increased dose leads to increased rate of cardiac-related deaths (Bradley et al. 2015b).

This unfortunate outcome leads to some area of controversy about the future treatment of locally advanced NSCLC. Investigators have shown that using midtreatment PET/CT to analyze response and direct dose escalation to regions of residual disease is feasible and can limit dose to normal tissues (Kong et al. 2007; Feng et al. 2009). Additionally, systemic therapy including targeted mutation-driven biologic agents for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK)-mutated tumors may improve survival. Immunologic agents in the category of anti-PD1 or anti-PD-L1 (programmed cell death protein 1 and programmed cell death ligand 1, respectively) checkpoint-directed therapies may also prove to be beneficial. Studies with these strategies are ongoing and hopefully will help direct the future of more individualized tumor-directed therapies.

Proton therapy is also currently being studied in a randomized Phase III trial. Proton therapy has shown in institutional series to be effective and has the potential for improved toxicity profile (Hoppe et al. 2012, 2016; Oshiro et al. 2012; Nguyen et al. 2015; Harada et al. 2016). Proton therapy could be most beneficial if indeed cardiac dose predicts for patient death. The role of proton therapy for many tumor sites, including thoracic malignancies, is controversial and should ideally be performed on a clinical trial.

Trimodality Therapy

In order to improve upon the local control and survival of single- or dual-modality therapies as previously described, Phase II studies were conducted by Albain et al. through the Southwest Oncology Group (SWOG) to study two treatment regimens for locally advanced NSCLC. The first regimen was trimodality therapy consisting of neoadjuvant concurrent ChemoRT followed by surgery, and the second regimen was definitive concurrent ChemoRT followed by adjuvant chemotherapy. Overall survival was promising, though morbidity and mortality rates were challenging for patients undergoing surgery (Albain et al. 1995, 2002). Albain et al. then compared these two regimens in a randomized trial of stage IIIA/IIIB resectable NSCLC patients. The trimodality arm demonstrated improved local control and progression-free survival, with a trend toward improved overall survival at 5 years of 27% vs. 20% ($p = 0.10$). Treatment-related deaths were greater in the trimodality arm and were found to be more prevalent in patients undergoing pneumonectomy (rather than lobectomy), especially right-sided pneumonectomy. Trimodality therapy was determined to be most beneficial for patients with single-station mediastinal nodal disease and those who are most likely to undergo lobectomy (Albain et al. 2009).

A study of the National Cancer Database (NCDB) of multimodality therapy for stage IIIA

NSCLC demonstrated improved survival for patients treated with trimodality therapy with lobectomy when compared to trimodality therapy with pneumonectomy, any surgery followed by adjuvant therapy, or definitive radiochemotherapy (Koshy et al. 2013). This further supports trimodality therapy with lobectomy as the optimal treatment for resectable stage III NSCLC.

Trimodality therapy for locally advanced NSCLC epitomizes the need for highly coordinated multimodality care. Since 45 Gy as given in the aforementioned trimodality studies is insufficient for a high probability of local control, surgical resectability must be determined at the time of diagnosis. Trying to use neoadjuvant ChemoRT to convert a patient from unresectable to resectable may result in breaks in treatment and suboptimal ChemoRT doses if the patient ultimately remains unresectable. To address this issue, several institutions treat to a definitive dose of about 60 Gy with concurrent chemotherapy prior to surgery. These studies show increased mediastinal clearance and pathologic complete response rate. They have not shown marked increase in postoperative morbidity or mortality (Sonett et al. 2004; Machtay et al. 2004; Cerfolio et al. 2005, 2009; Shumway et al. 2011). A study of the NCDB reviewed low- (36–44 Gy), intermediate- (45–54 Gy), and high-dose (55–74 Gy) neoadjuvant radiotherapy. This study showed improved survival with the intermediate neoadjuvant radiotherapy dose group. Selection bias could explain why higher doses lead to inferior survival since these patients may have had bulkier disease or been at higher risk to require more extensive surgery (Sher et al. 2015).

Pless et al. reported a Phase III trial of neoadjuvant chemotherapy vs. neoadjuvant ChemoRT for stage IIIA/B NSCLC. The trial showed no difference in event-free survival (primary endpoint) or overall survival and was stopped early due to futility. About 15% in the trimodality arm did not receive radiation therapy though, and 15% in the neoadjuvant chemotherapy only arm did receive radiation therapy. With the available data at the time of study design, median event-free survival was estimated to be 18 months with trimodality therapy (Pless et al. 2015). Other large randomized studies of trimodality therapy and definitive ChemoRT report progression-free survival of about 12 months, so this study may have set a lofty goal for the trimodality arm (Curran et al. 2011; Bradley et al. 2015b; Albain et al. 2009). Debate exists, nevertheless, about whether trimodality therapy should be favored over neoadjuvant chemotherapy for stage III resectable patients.

Superior sulcus tumors may be difficult to treat surgically due to their frequent involvement of the brachial plexus, subclavian vessels, and spine. SWOG 9416 was a Phase II study of a similar trimodality therapy regimen for NSCLC of the superior sulcus. The regimen involved treating the tumor and ipsilateral supraclavicular fossa (but not the mediastinum or hila) to 45 Gy with concurrent cisplatin and etoposide chemotherapy followed by surgical resection 3–5 weeks later. With this regimen, 5-year survival was 44% for all patients and 54% for those where a complete resection could be performed (Rusch et al. 2007).

With all of the available data for clinical stage III NSCLC patients, there are three primary curative-intent approaches – trimodality therapy, definitive ChemoRT, and chemotherapy followed by surgery. Patients must obviously be operative candidates to consider a surgical option, and the choice between trimodality therapy and chemotherapy followed by surgery is primarily institution dependent. Definitive ChemoRT is optimal for patients who are poor surgical candidates due to either medical comorbidities, required surgery would leave the patient with inadequate pulmonary function, or high-volume nodal disease.

Locally Advanced with Poor Performance Status

Treatment options for patients with locally advanced NSCLC were described in the previous section. Patients who are medically unfit or unwilling to undergo one of these standard regimens may be considered for treatment with definitive therapy with sequential systemic therapy followed by radiotherapy or radiation therapy alone.

As part of the evolution of treatment of locally advanced NSCLC, chemotherapy was

investigated – first sequentially and then concurrently. Sequential chemotherapy followed by radiotherapy was shown to improve survival when compared to radiotherapy alone (Sause et al. 1995, 2000; Dillman et al. 1990, 1996). Concurrent ChemoRT subsequently was shown to improve survival compared to sequential therapy but with increased toxicity (Curran et al. 2011; Auperin et al. 2010). For patients who are unlikely to tolerate concurrent ChemoRT, sequential therapy should still be considered over radiotherapy alone.

Historically, doses of radiation therapy of 60 Gy in 30 fractions were determined to have improved overall survival compared to lower doses (Perez et al. 1980). Institutional and cooperative group studies have studied increased total dose and/or increased dose per fraction. These studies showed mixed results regarding local control but with potentially increased toxicity and have not led to subsequent randomized trials (Bradley et al. 2005a). Altered fractionation schedules such as continuous hyperfractionated accelerated radiation therapy (CHART) showed no difference when compared to standard fractionation (Saunders et al. 1999; Baumann et al. 2011). Single-institution studies have studied hypofractionated courses for patients who are not candidates for chemotherapy. A retrospective study comparing a hypofractionation regimen of 45 Gy in 15 fractions showed no difference in local control or survival when compared to standard fractionation (Amini et al. 2012a). Using advanced techniques like intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost has demonstrated a reasonable toxicity profile but with failure still tending to occur in the high-dose region (Swanick et al. 2015).

Proton therapy has been used with potential for dose escalation while still maintaining a reasonable toxicity profile for unfavorable patients, even though ultimate prognosis remains poor (Oshiro et al. 2012). Proton therapy has additionally been delivered with a hypofractionated regimen of 45–60 Gy in 15 fractions which was well tolerated (Gomez et al. 2013a). There is no clear standard of care for patients with locally advanced NSCLC who are unable to receive chemotherapy, but it is reasonable to deliver doses of about 60 Gy in 2 Gy fractions or a biologically equivalent altered fractionation schedule.

Postoperative Radiation Therapy

Postoperative radiation therapy (PORT) for various pathological stages has been quite controversial over the past decades. A commonly cited study that demonstrates this controversy is the PORT meta-analysis. The PORT meta-analysis found poorer survival with PORT in patients with N0/N1 disease and no impact on survival for patients with N2 disease. This study was published in 1998 and 2005 and contained studies whose recruitment began between 1966 and 1988. Therefore, the treatment techniques routinely comprised orthovoltage or cobalt-60 with two-dimensional treatment planning (Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group 1998; Group PM-aT 2005).

Modern studies for resected lung cancer show a decrease in local recurrence with potential for improved overall survival with addition of PORT for patients with advanced nodal disease (Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. The Lung Cancer Study Group 1986; Stephens et al. 1996; Mayer et al. 1997; Feng et al. 2000; Douillard et al. 2008). Studies that comprised mostly early-stage patients showed no difference in local recurrence often with poorer survival in the group that received PORT (Van Houtte et al. 1980; Dautzenberg et al. 1999).

RTOG 9705 was a Phase II study which treated resected stage II and IIIA NSCLC with PORT and concurrent chemotherapy. The dose was 50.4 Gy in 28 fractions to the mediastinum and ipsilateral hilum, but the primary tumor bed was treated only if parietal pleura was pathologically invaded. A boost to 59.4 Gy was delivered for extracapsular extension of nodal disease and T3 disease. They reported median survival of 56.3 months with a toxicity profile which

compared favorably to historical controls. The mediastinal fields in this study were fairly large, extending from the thoracic inlet to a range of 5–8 cm inferior to the carina (Bradley et al. 2005b). The Lung Adjuvant Radiotherapy Trial (Lung ART) study is ongoing and randomizes patients to PORT vs. no PORT for completely resected N2 disease. They are also investigating smaller target volumes to treat one nodal station proximal and distal to the involved nodal station(s) (Le Pechoux et al. 2007; Spoelstra et al. 2010). A study of the NCDB reported on more modern radiation therapy from 1998 to 2006 and showed improved survival with PORT for completely resected N2 NSCLC (Corso et al. 2015). Another NCDB study showed improved survival with PORT for patients with positive surgical margins, regardless of nodal stage (Wang et al. 2015). Amini et al. reported on their institutional series of patients treated with neoadjuvant chemotherapy followed by surgery with persistent mediastinal nodal disease. With a median follow-up time of 28.1 months, the addition of PORT resulted in a locoregional failure rate of 16.4%. They also found that addition of adjuvant chemotherapy improved the distant metastasis rate and overall survival (Amini et al. 2012b).

Most of these studies describe PORT for completely resected NSCLC; however, patients with incompletely resected NSCLC have a more clear indication for PORT. The use of concurrent chemotherapy with PORT vs. sequential chemotherapy and PORT is an additional controversial topic. A study from Zhou et al. treated patients with positive surgical margins with concurrent ChemoRT to a median dose of 60 Gy. With a median follow-up time of 40 months, they reported a local recurrence rate of 19.6% (Zhou et al. 2015). Lee et al. compared their institutional experience of PORT alone to concurrent PORT with chemotherapy and showed that local control and disease-free survival were improved with the addition of concurrent chemotherapy (Lee et al. 2014). A Phase II study by Gomez et al. treated postoperative superior sulcus tumors with concurrent chemotherapy and PORT and demonstrated a 10-year locoregional control rate of 76% (Gomez et al. 2012).

The more modern series support the use of PORT for completely resected N2 or incompletely resected NSCLC of any stage. The use of more limited volume PORT will be studied as part of the current Lung ART study.

1.2 Small Cell Lung Cancer

Small cell lung cancer (SCLC) comprises 10–15% of all lung cancer diagnoses and has the predilection to be metastatic at the time of diagnosis and for brain metastases to be part of the eventual pattern of spread during the patient's treatment course. This section aims to describe the treatment and controversies regarding both limited stage (LS-) and extensive stage (ES-) SCLC.

1.2.1 Limited Stage SCLC

The history of LS-SCLC nicely progresses over time with studies showing that combined modality therapy with concurrent chemotherapy and radiation therapy followed by prophylactic cranial irradiation (PCI) should be the standard management. Studies progressed from chemotherapy or radiation therapy alone to sequential chemotherapy and radiation therapy to concurrent ChemoRT to concurrent ChemoRT followed by PCI (Radiotherapy alone or with chemotherapy in the treatment of small-cell carcinoma of the lung. Medical Research Council Lung Cancer Working Party 1979; Radiotherapy alone or with chemotherapy in the treatment of small-cell carcinoma of the lung: the results at 36 months. 2nd report to the Medical Research Council on the 2nd small-cell study 1981; Perry et al. 1987; Pignon et al. 1992; Auperin et al. 1999; Turrisi et al. 1999). However, there still remain several controversial issues in the management of LS-SCLC, especially since 5-year survival is still poor.

Radiation Dose Fractionation

Fractionation of radiation therapy is a common debate in the treatment of LS-SCLC. The first major randomized trial of radiation therapy fractionation reported by Turrisi et al. compared

45 Gy in 25 fractions of 1.8 Gy daily to 45 Gy in 30 fractions of 1.5 Gy twice daily with concurrent cisplatin/etoposide chemotherapy followed by PCI. They showed improved survival with 45 Gy delivered twice daily over 3 weeks. There was increased high-grade toxicity, primarily esophagitis, with this regimen though (Turrisi et al. 1999). This study is not truly a study of fractionation regimen but rather a dose-escalation study since the twice-daily regimen is more biologically effective. Cooperative groups initially studied other regimens though not in Phase III randomized trials. The Phase II CALGB study used 70 Gy in 35 fractions with concurrent chemotherapy and reported outcomes similar to those reported in the twice-daily arm of the Turrisi et al. study (Bogart et al. 2004). RTOG 0239 studied accelerated high-dose radiotherapy with chemotherapy delivered to a dose of 61.2 Gy over 5 weeks with 28.8 Gy in 1.8 Gy daily fractions on days 1–22. On treatment days 23–26, the same plan was delivered each morning, and an off-cord boost delivered at least 6 h later. The remainder of the plan delivered the off-cord boost twice daily to complete the course. They showed higher than expected local control and lower than expected toxicity, though survival was not superior to the twice-daily arm from the Turrisi et al. study (Komaki et al. 2012).

More recently, randomized trials began comparing once-daily vs. twice-daily radiation therapy. The CALGB/RTOG ongoing study is comparing 45 Gy in 30 twice-daily fractions to 70 Gy in 35 daily fractions. This study originally also contained the RTOG 0239 regimen as described above, but this arm was discontinued (per design of the study) due to greater toxicity when compared to 70 Gy in 35 fractions (Alliance for Clinical Trials in Oncology – CALGB 30610/RTOG 0538 – Phase III Comparison of Thoracic Radiotherapy Regimens in Patients with Limited Stage Small Cell Lung Cancer also Receiving Cisplatin or Carboplatin and Etoposide). The CONVERT trial compared the same twice-daily regimen of 45 Gy in 30 fractions to 66 Gy in 33 daily fractions. This study was reported in 2016 and showed median survivals of 30 months and 25 months ($p = 0.15$) with twice-daily and daily fractionation, respectively. Toxicity rates were also comparable except for grade 3/4 neutropenia which was increased with the twice-daily regimen (74% vs. 64%, $p = 0.03$). There were no significant differences in febrile neutropenia, esophagitis, and pneumonitis between the two regimens. This data supports the use of either regimen for the treatment of LS-SCLC (Faivre-Finn et al. 2016a, b). The results of the currently accruing CALGB/RTOG study will be important to correlate with the CONVERT study to inform on the proper radiotherapy regimen for the treatment of limited stage SCLC. The reported dose-fractionation regimens and results of ChemoRT for LS-SCLC are described in Table 3.

Elective Nodal Irradiation

Treatment fields have also been a topic of debate over the years. The Turrisi et al. study treated the tumor and the bilateral mediastinal and ipsilateral hilar lymph nodes (Turrisi et al. 1999). Other prospective studies also included elective nodal irradiation (ENI) (Bogart et al. 2004; Komaki et al. 2012). The driving force behind omission of ENI is the potential for increased toxicity associated with increased thoracic radiotherapy volumes. A study by De Ruysscher et al. reported on patients who were staged with CT only and treated with omission of ENI. They found 3 of 27 (11%) patients failed outside of the PTV, all in the ipsilateral supraclavicular fossa (De Ruysscher et al. 2006). A similar study by Colaco et al. reported on 38 patients treated without ENI again in the era of CT-only staging. They found that only 2 of 38 patients (5%) failed outside of the PTV in the elective nodal region, and both of those patients had distant metastases diagnosed concurrently (Colaco et al. 2012). When similar studies were performed in the era of PET/CT staging, isolated nodal failures occurred in <5% of cases with improved rates of esophagitis (van Loon et al. 2010; Hu et al. 2012). Han et al. compared survival and progression-free survival for patients treated with or without ENI and found no difference in outcomes. Patients who were not staged with PET/CT had inferior survival if they were treated with omission of ENI in their study (Han et al. 2012).

Table 3 Dose-fractionation schedules and outcomes for limited stage small-cell lung cancer

Author (year)	Thoracic radiotherapy dose (Gy)	Chemotherapy	Sequence	Number of patients	Median survival (months)	2-year overall survival (%)	5-year overall survival
Turrisi et al. (1999)	45 Gy (1.8 Gy daily over 25 fractions) 45 Gy (1.5 Gy BID over 30 fractions)	Cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1–3 q3weeks × four cycles	Concurrent ChemoRT starting on day 1, cycle 1 of chemotherapy	206 211	19 23	41% 47%	16% 26%
Bogart et al. (2004)	70 Gy (2 Gy daily over 7 weeks)	Induction topotecan 1 mg/m^2 on days 1–5 and 22–26 and paclitaxel 175 mg/m^2 on days 1 and 22 Carboplatin (AUC = 5) on days 43, 64, and 85 and etoposide 100 mg/m^2 on days 42–44, 64–66, and 85–87	RT started on day 43 – first day of carboplatin and etoposide chemotherapy	63	22.4	48%	Not reported
Komaki et al. (2012)	61.2 Gy (1.8 Gy daily on days 1–22 and then 1.8 Gy BID on days 23–33)	Cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1–3 q3weeks × four cycles	RT started on day 1, cycle 1 of chemotherapy	71	19	36.6%	Not reported
Faivre-Finn et al. (2016b)	45 Gy (1.5 Gy BID over 30 fractions) 66 Gy (2 Gy daily over 33 fractions)	Cisplatin 25 mg/m^2 days 1–3 or 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1–3 × 4–6 cycles	RT started on day 22 of cycle 1 of chemotherapy	274 273	30 25	56% 51%	Not reported

In a prospective study by Bradley et al., PET upstaged 3 of 24 (12.5%) patients from limited to extensive stage, thus altering the goals of care. PET identified additional sites of nodal disease in six (25%) patients resulting in altered treatment plans (Bradley et al. 2004). PET is not only important for nodal target volume delineation but also crucial for accurate staging of distant disease.

Prophylactic Cranial Irradiation

PCI is routinely indicated for patients who have responded to concurrent ChemoRT. The Auperin et al. meta-analysis of PCI for LS-SCLC showed improved overall survival of about 5% (Auperin et al. 1999). The dose of PCI has been debated and multiple fractionation schedules have been used. Le Pechoux et al. evaluated the question of PCI dose in a randomized study of high-dose (36 Gy at 2 Gy daily or 1.5 Gy twice daily) vs. low-dose (25 Gy at 2.5 Gy daily) PCI. They showed no difference in incidence of brain metastases but showed an increase in mortality in the high-dose PCI arm (likely due to an unrelated increase in disease progression) (Le Pechoux et al. 2009). A study of the Surveillance, Epidemiology, and End Results (SEER) database limited to elderly patients (≥70 years old) maintained that PCI was an independent predictor for improved OS in patients with LS-SCLC (Eaton et al. 2013). A survey of PCI use demonstrated increasing, but still quite low, percentages of patients were receiving PCI. In 2006–2007, only 49% of patients with LS-SCLC received PCI (Komaki et al. 2013).

Hippocampal-sparing whole-brain irradiation for PCI is an area of ongoing study. The goal of hippocampal avoidance is to decrease neurocognitive deficits that are a known potential side effect of whole-brain radiotherapy. In SCLC, data suggest that brain metastases occur within the region of hippocampal avoidance in only about 5% of cases (Kundapur et al. 2015). Hippocampal avoidance PCI is currently being investigated in a randomized Phase III trial (NRG-CC003: A Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer). PCI should routinely be offered to limited stage SCLC patients who have responded to ChemoRT. The role of hippocampal avoidance to potentially decrease neurocognitive deficits is exciting but investigational at this time.

1.2.2 Extensive Stage SCLC

ES-SCLC is primarily managed with chemotherapy, but radiation therapy has a few specific roles for these patients. At diagnosis, palliative radiation therapy may be required for the treatment of brain metastases, superior vena cava (SVC) syndrome, or obstructive respiratory symptoms. These scenarios are common given the predilection of SCLC to metastasize to the brain or for bulky thoracic disease to cause compressive symptoms.

Prophylactic Cranial Irradiation

There has been significant debate regarding the role of PCI for patients with ES-SCLC without brain metastases. This question was addressed in a European Organisation for Research and Treatment of Cancer (EORTC) Phase III randomized trial of ES-SCLC with response to chemotherapy to receive or not receive PCI. PCI significantly improved 1-year OS from 13% to 27% with addition of PCI. PCI also significantly decreased the 1-year incidence of symptomatic brain metastases from 40% to 15% ($p < 0.001$). The median survival was improved from 5.4 to 6.7 months ($p = 0.003$) with PCI which could either support or detract the value of PCI since, though statistically significant, the improvement in median survival is just over 1 month (Slotman et al. 2007). A similar Japanese study of ES-SCLC patients treated with chemotherapy randomized patients to receive PCI or observation. This study required restaging of the brain with magnetic resonance imaging (MRI) prior to PCI, which is different than the EORTC study. They showed a trend for improved median survival of 15.1 months vs. 10.1 months ($p = 0.09$) with observation and PCI, respectively, showing a potentially conflicting result to the EORTC study. They showed no difference in grade 2 toxicities in this study (Seto et al. 2014).

Any potential benefit of PCI should be balanced by potential effect on patients' quality of life (QOL). The EORTC study assessed QOL as

part of their study, and they showed that PCI decreased the health-related QOL metrics of fatigue and hair loss. Decreased functional metrics and global health status were more limited with addition of PCI (Slotman et al. 2009). The risks and benefits of PCI should be discussed with patients so they can make an informed decision.

Consolidation Radiotherapy

In an attempt to improve survival for patients with ES-SCLC, studies of dose intensification with chemotherapy were conducted. These studies showed increased toxicity with chemotherapy dose intensification without improvement in overall survival (Giaccone et al. 1993; Ihde et al. 1994; Mavroudis et al. 2001). Thoracic progression of disease in ES-SCLC is common, occurring in about 90% of patients within the first year of diagnosis, which is often life threatening (Slotman et al. 2007). In an attempt to improve survival with local therapy, Jeremic et al. studied patients with ES-SCLC treated with three cycles of cisplatin and etoposide with complete distant response and complete or partial local response. Patients were randomized to either thoracic radiation therapy (TRT) 54 Gy in 36 fractions twice daily with concurrent chemotherapy vs. chemotherapy alone. Both groups also received PCI. They showed significant improvement of median survival (17 vs. 11 months) and 5-year survival (9.1% vs. 3.7%, $p = 0.041$) with addition of TRT (Jeremic et al. 1999a). In a similar study by Slotman et al., patients who had any response to chemotherapy were randomized to PCI vs. PCI and TRT 30 Gy in ten fractions. Patients receiving TRT had a trend toward improved 1-year survival (33% vs. 28%, $p = 0.066$) with secondary analysis showing increased 2-year survival (13% vs. 3%, $p = 0.004$) (Slotman et al. 2015). A meta-analysis of TRT for ES-SCLC was performed and included these two randomized trials. They reported improved survival and progression-free survival with addition of TRT. Grade ≥3 esophageal toxicity is higher with TRT though (6.6% vs. 0%, $p < 0.001$) (Palma et al. 2015).

Further analysis of the Slotman et al. study of TRT found that patients with residual thoracic disease after chemotherapy had improved survival with addition of TRT, whereas patients with complete thoracic response to chemotherapy experienced no benefit with TRT. They conclude that TRT should be offered to patients with favorable but incomplete response to chemotherapy, and TRT should be omitted for patients with complete thoracic response (Slotman and van Tinteren 2015).

If TRT is to be given, there is no clear evidence how it should be sequenced. It reasons that if TRT is to be given, then the sequence of therapy should replicate either Phase III trial described above. In Jeremic et al., PCI was delivered after TRT which is logical since chemotherapy was given concurrently with TRT in that study (Jeremic et al. 1999a). In Slotman et al., PCI was delivered concurrently with TRT in 88% of patients and appeared to be well tolerated. This is a more convenient approach for the patient since both regimens are commonly delivered in ten fractions over 2 weeks (Slotman et al. 2015). Now with two randomized trials supporting consolidation TRT for ES-SCLC, TRT should be routinely delivered for patients with favorable, but incomplete, thoracic response to chemotherapy.

Another therapy that has been investigated in an attempt to improve survival for patients with ES-SCLC is delivery of consolidation radiation therapy to the local disease and sites of distant metastases. The role of extracranial consolidation was studied in RTOG 0937 which was a randomized Phase II study of chemotherapy followed by PCI with or without consolidation radiation to metastatic sites. Consolidation radiation delayed disease progression, but it did not improve survival (Gore et al. 2016). These data support PCI with TRT for ES-SCLC patients with a favorable but incomplete response to chemotherapy.

1.3 Recurrent Lung Cancer

Local or nodal recurrences of lung cancer are serious, but potentially salvageable, scenarios. For patients who are willing and able to pursue aggressive therapy, radiation therapy can be employed with the goal to salvage the recurrence after prior surgery or local radiotherapy.

1.3.1 Salvage Radiotherapy for Surgical Treatment Failures

Surgical resection is the standard curative-intent treatment for early stages of NSCLC and may be a component of multimodality therapy for locally advanced NSCLC. As described previously, even for T1 lesions, the Lung Cancer Study Group trial showed local recurrence rates of 6% with lobectomy and 17% with sublobar resection (Ginsberg and Rubinstein 1995). However, postoperative recurrence of NSCLC occurs in up to 45% of patients following resection. Locoregional recurrence is the first site of recurrence in 19% of surgical cases and should be treated like unresectable stage III NSCLC (Yano et al. 2014). The median overall survival for a locoregional recurrence ranges from 14 to 19 months for patients treated with salvage radiotherapy (Kagami et al. 1998; Jeremic et al. 1999b; Tada et al. 2005). In a 2005 retrospective study, Tada et al. evaluated 31 patients with recurrent NSCLC treated to a prescribed dose of 60 Gy in 30 fractions (Tada et al. 2005). A complete radiographic response was seen in 23% of the patients, and a partial response was seen in 64% of the patients. The 1-year, 2-year, and 4-year overall survival rates were 61%, 30%, and 15%, respectively (Tada et al. 2005). In a retrospective analysis of three-dimensional conformal radiotherapy for postoperative thoracic lymph node recurrence of NSCLC, the median overall survival was 37.3 months (Okami et al. 2013). In contrast, the median overall survival for patients with lymph node recurrence who received chemotherapy, an EGFR inhibitor, or supportive care was only 14.6 months. Radiotherapy, often combined with concurrent chemotherapy, can salvage surgical recurrences, and long-term survival is possible.

Salvage SBRT has also been used for postoperative locoregional recurrence in NSCLC patients. An Italian retrospective study reviewed the outcomes of 28 patients who underwent salvage SBRT for locoregional recurrence of NSCLC (Agolli et al. 2015). The prescribed doses were 23 Gy in one fraction for mediastinal nodal recurrences, 30 Gy in one fraction for peripheral or small tumors (<30 cm^3), or 45 Gy in three fractions for centrally located or large tumors (≥ 30 cm^3). Complete and partial responses were observed in 16% and 70% of patients, respectively. Local control at 1 and 2 years was 96.6% and 84.7%, respectively, and the median overall survival was 31 months (Agolli et al. 2015). Takeda et al. reported a 2-year overall survival of 76.4% in NSCLC patients treated with SBRT for isolated postoperative local recurrences (Takeda et al. 2013).

1.3.2 Salvage SBRT for Radiotherapy Treatment Failures

High-dose conventionally fractionated radiotherapy and SBRT have been used as salvage therapy for locoregional recurrences following ChemoRT or SBRT (Amini et al. 2014; De Ruysscher et al. 2014; Griffioen et al. 2014; Tetar et al. 2015). After definitive radiotherapy, the 2-year local recurrence rate is 20–44%, and in most of these cases, the recurrent tumor is not resectable (Vansteenkiste et al. 2013). With systemic therapy alone for these locoregional recurrences, median overall survival is 10–12 months (De Ruysscher et al. 2014). With re-irradiation, the median overall survival is approximately 17 months for locally recurrent NSCLC, though patients are at potentially increased risk for toxicity including radiation pneumonitis, fibrosis, and bleeding (De Ruysscher et al. 2014). In a meta-analysis of re-irradiation by De Ruysscher et al., the risk of grade 3–4 lung toxicity after re-irradiation is only 10% (De Ruysscher et al. 2014).

Salvage radiotherapy with SBRT may be the only reasonable option for potential salvage of a local failure. In patients treated with SBRT for local recurrences following conventional radiotherapy, local control ranges from 65% to 92%, and the 1-year overall survival following salvage SBRT is 59–80% (Amini et al. 2014). Hearn et al. reported on the safety of salvage SBRT for local recurrences of NSCLC after primary SBRT. Ten patients received salvage SBRT for recurrence to a dose of 50 Gy in five fractions and 60 Gy in three fractions for central and peripheral tumors, respectively. No patient experienced grade 3–5 toxicity (Hearn et al. 2014). Results of such retrospective and exploratory studies suggest that repeat SBRT is a safe and effective treatment for well-selected patients.

1.4 Palliative Radiotherapy

Palliative radiation therapy for lung cancer may be necessary to control hemoptysis, chest wall pain, superior vena cava (SVC) syndrome, or airway obstruction. Several evidence-based guidelines exist regarding the appropriate management for the palliation of intrathoracic lung cancer (Rodrigues et al. 2011, 2012a, b, 2013). The decision to offer palliative radiotherapy depends on the patient's performance status, disease status, pulmonary function, treatment volume, symptomatology, and overall prognosis. Palliative radiotherapy is generally reserved for patients presenting with or at risk for any of the aforementioned symptoms (Rodrigues et al. 2012b).

1.4.1 Pulmonary Symptoms

A standard regimen for palliation of local symptoms from lung cancer is 30 Gy in ten fractions. However, multiple radiotherapy regimens ranging from 10 Gy in one fraction to 60 Gy in 30 fractions over 6 weeks have been used to treat patients with thoracic symptoms from NSCLC (Stevens et al. 2015). Kramer et al. randomized 297 patients with inoperable stage IIIA/B or stage IV NSCLC with thoracic symptoms (excluding SVC syndrome) to either 30 Gy in ten fractions or 16 Gy in two fractions (Kramer et al. 2005). The duration of symptom improvement was significantly longer with 30 Gy in ten fractions, persisting for 22 weeks, compared to only 12 weeks with 16 Gy in two fractions. Additionally, 1-year overall survival was significantly higher with 30 Gy in ten fractions vs. 16 Gy in two fractions (19.6% vs. 10.9%, $p = 0.03$) (Kramer et al. 2005). In a study of 30 Gy in ten fractions and 10 Gy in one fraction for palliation of thoracic symptoms from lung cancer, symptomatic improvement was significantly greater in the 30 Gy in ten-fraction arm (Erridge et al. 2005). In a comparison of 10 Gy in one fraction and 20 Gy in five fractions, there was no significant difference in the palliation of thoracic symptoms from lung cancer (Bezjak et al. 2002). However, Bezjak et al. demonstrated that patients treated with a palliative regimen of 20 Gy in five fractions had significantly improved overall survival compared to those treated with 10 Gy in one fraction (Bezjak et al. 2002). Hypofractionated palliative radiotherapy schedules can be used for patients with poor performance status or those requiring a shorter treatment course due to poor prognosis (Rodrigues et al. 2011; Reinfuss et al. 2011).

Two meta-analyses showed that total dose and number of fractions did not significantly affect palliation of thoracic symptoms or overall survival in patients with NSCLC (Stevens et al. 2015; Ma et al. 2014). In a meta-analysis by Ma et al., there was no difference in palliation of cough, chest pain, or hemoptysis with higher total doses (≥30 Gy) compared to lower doses (<30 Gy). Additionally, 1 and 2-year overall survival was not significantly different between the higher and lower total radiation doses (Ma et al. 2014). A Cochrane review from 2015 indicated that the number of fractions used for palliative radiotherapy had no significant effect on 1-year overall survival in patients with either good or poor performance status. The risk of esophagitis, radiation myelopathy, and pneumonitis did not significantly differ based on the number of fractions either (Stevens et al. 2015). A meta-analysis by Fairchild et al. in 2008 showed improved 1-year overall survival in patients treated with a BED of ≥35 $Gy_{\alpha/\beta = 10}$ compared to patients treated with a lower BED. Furthermore, a palliative dose with a BED of ≥35 Gy was more likely to result in any symptomatic improvement vs. a lower BED (Fairchild et al. 2008). Several criticisms of this meta-analysis have been reported in the 2015 Cochrane review though (Stevens et al. 2015). Thus, it is possible that the reported benefits in survival and symptom improvement were due to study design rather than differences in BED.

There is no clear benefit of administering chemotherapy concurrently with radiation for the palliation of thoracic symptoms due to lung cancer (Rodrigues et al. 2011). In a Phase III study of NSCLC patients randomized to either palliative radiotherapy (20 Gy in five fractions) or the same palliative radiotherapy plus concurrent fluorouracil, there was no significant difference in overall or progression-free survival or in palliation of symptoms (Ball et al. 1997). Patients treated with radiotherapy plus fluorouracil were significantly more likely to have acute toxicity,

including nausea, vomiting, esophagitis, stomatitis, and skin reaction. It reasons to individualize dose of palliative radiotherapy to the individual patient and clinical scenario.

1.4.2 Endobronchial Brachytherapy

Endobronchial brachytherapy (EBB) has been used for the palliation of symptoms caused by lung tumors including hemoptysis, obstruction, dyspnea, and cough (Skowronek 2015). This procedure involves bronchoscopy with placement of an afterloading catheter in the airway adjacent to the tumor. There are no randomized trials to recommend EBB either alone or combined with another treatment in the routine initial palliation of symptoms secondary to lung cancer (Rodrigues et al. 2011; Rosenzweig et al. 2013). A Cochrane review from 2012 included NSCLC patients from 14 trials comparing several palliation treatment techniques including EBB, EBRT alone, EBB plus EBRT, EBB plus chemotherapy, and laser therapy. The authors demonstrated that EBRT provides more effective palliation than EBB alone and that there was no improvement in overall survival with EBB compared to EBRT or laser therapy (Reveiz et al. 2012). EBB is generally reserved for symptomatic patients with recurrent endobronchial obstructing or bleeding tumors after prior EBRT.

1.4.3 Superior Vena Cava Syndrome

SVC syndrome arises from extrinsic or intrinsic obstruction of blood flow through the superior vena cava. Symptoms of SVC syndrome include swelling of the face, neck, and upper extremity, cough, dyspnea, stridor, and altered mental status (Rice et al. 2006). While the prevalence of SVC syndrome secondary to intravascular devices has increased over the past 20 years (Cheng 2009), intrathoracic malignancies still remain the most common cause of SVC syndrome (Straka et al. 2016). NSCLC accounts for the majority of malignant causes of SVC syndrome (Straka et al. 2016; Wilson et al. 2007).

Historically, all cases of SVC syndrome were classified as an oncologic emergency requiring immediate management (Schechter 1954). Indeed, laryngeal constriction and cerebral edema secondary to SVC syndrome are life threatening and require emergent treatment (Straka et al. 2016; Sofue et al. 2013). Only about 5% of patients with SVC syndrome present with the aforementioned life-threatening conditions and require emergent treatment with a venogram and stent placement (Yu et al. 2008). Emergent radiotherapy is not a first-line treatment in life-threatening cases of SVC syndrome, as palliation is more rapid with intravascular stenting (Nicholson et al. 1997).

Most cases of SVC syndrome are relatively benign, and appropriate workup and staging can be performed (Straka et al. 2016; Wilson et al. 2007; Yu et al. 2008). Following appropriate diagnosis and staging, palliative or curative intent radiotherapy or ChemoRT is still considered the primary treatment modality for SVC syndrome. A Cochrane review meta-analysis has reported that in patients with SVC syndrome secondary to NSCLC or SCLC, chemotherapy and/or radiotherapy successfully palliates SVC compressive symptoms in the majority of cases. Insertion of an SVC stent improved symptoms in 95% of cases (Rowell and Gleeson 2001). The time to symptom relief has been reported to be 3–30 days (Straka et al. 2016).

Several fractionation regimens may be utilized for palliation of SVC syndrome including 3–4 Gy for the first 2–5 fractions followed by conventional 2 Gy fractionation to a definitive dose based on the tumor histology (Straka et al. 2016; Davenport et al. 1978; Armstrong et al. 1987; Egelmeers et al. 1996). A hypofractionated regimen of 12 Gy in two fractions has been demonstrated to induce a complete symptom alleviation in 74% of patients with SVC syndrome (Lonardi et al. 2002). Palliative hypofractionated radiotherapy and definitive ChemoRT can be used in the management of SVC syndrome based on the goals and intent of disease management.

2 Thymoma

Thymomas are rare tumors of the thymus gland with a reported incidence of 0.13–0.17 per 100,000 person-years (Engels 2010; Scorsetti

et al. 2016). The incidence of thymomas in men and women is similar, and the incidence increases with age through the eighth decade of life (Engels 2010; Scorsetti et al. 2016; Kim and Thomas 2015).

Thymomas most commonly occur in the anterior-superior mediastinum and comprise approximately 50% of all anterior mediastinal tumors (Scorsetti et al. 2016). Thymomas arise from epithelial cells in the thymus. Because the thymus is the site of T-cell maturation, thymomas are associated with multiple autoimmune syndromes including myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, and polymyositis (Scorsetti et al. 2016). Approximately 30–50% of thymoma patients have concurrent myasthenia gravis. In a retrospective study from Italy, multivariate analysis showed that myasthenia gravis in thymoma patients had no significant effect on overall survival or recurrence (Filosso et al. 2015). Patients with thymoma also have about an 8–28% increased risk of developing a secondary malignancy, most notably non-Hodgkin lymphoma (Engels and Pfeiffer 2003; Filosso et al. 2013). It is hypothesized that immune dysregulation from thymomas increases the risk of secondary malignancies (Welsh et al. 2000).

Histologic classification of thymomas is based on morphology and the lymphocyte/epithelial cell ratio with six different designations of thymomas (A, AB, B1, B2, B3, and C) as set forth by the World Health Organization (WHO) and detailed in Table 4 (Scorsetti et al. 2016). Type A thymomas are spindle cell or medullary thymomas with rare lymphocytes and no nuclear atypia. In contrast, type C lesions are heterogeneous thymic carcinomas with significant cytologic atypia, and mature lymphocytes and plasma cells present between tumor lobules. Prognosis worsens as thymomas progress from A to C histologic subtype. The 10-year overall survival for types A-B1

Table 4 Histologic classification of thymic tumors

WHO histologic classification	
Type A	
Tumor composed mainly of epithelial cells with spindle/oval shape, lacking nuclear atypia; lymphocytes are rare	Spindle cell or medullary thymoma
Type AB	
Tumor in which foci with features of type A thymoma are admixed with lymphocyte-rich areas: the segregation of two patterns can be sharp or indistinct	Mixed thymoma
Type B1	
Tumor that resembles the normal functional thymus, combining predominant areas resembling normal thymic cortex and areas resembling thymic medulla. This is a thymoma "lymphocyte predominant thymoma" and the neoplastic epithelial cells are scant, small, with little atypia	Organoid, lymphocyte rich or lymphocytic or predominantly cortical thymoma
Type B2	
Tumor in which the neoplastic epithelial component (plump cells with vesicular nuclei and conspicuous nucleoli) is scattered individually or in small clusters among immature lymphocytes	Cortical thymoma
Type B3	
Tumor composed predominantly of epithelial cells with a round or polygonal shape and exhibiting mild atypia, admixed with a minor component of immature lymphocytes	Well-differentiated thymic carcinoma or epithelial thymoma or squamoid thymoma
Type C	
Tumor exhibiting clear-cut cytologic atypia and lacking a significant number of immature interepithelial thymocytes. Mature lymphocytes and plasma cells are present in the septa between tumor lobules and in the tumor periphery. This subtype is usually indistinguishable from extrathymic carcinomas	Heterogeneous thymic carcinoma

Scorsetti et al. (2016)

thymomas is over 90% (Quintanilla-Martinez et al. 1994; Chen et al. 2002). However, for type B2, B3, and C lesions, the 5-year overall survival is 75%, 70%, and 48%, respectively (Scorsetti et al. 2016).

Staging of thymomas is based on the Masaoka system, initially proposed in 1981, with modifications in 1994 and 2011 (Masaoka et al. 1981; Koga et al. 1994; Detterbeck et al. 2011). The Masaoka staging system is shown in Table 5. Tumor stage and completeness of resection are the most important prognostic factors for thymomas (Scorsetti et al. 2016; Detterbeck and Parsons 2004). Five-year overall survival in stage I and II patients with a complete surgical resection is 90% (Scorsetti et al. 2016; Regnard et al. 1996). Stage III and IV patients with a complete surgical resection have reported 5-year overall survivals of 60% and 25%, respectively (Regnard et al. 1996). Only about 11% of thymoma patients present with stage IV disease, and 1–2% present with lymph node metastases (Scorsetti et al. 2016; Kondo and Monden 2003).

After concomitant diseases such as myasthenia gravis have been stabilized, surgery is the primary treatment for thymomas, with the goal of a complete en bloc resection. Median sternotomy is the standard approach for thymectomy (Toker

Table 5 Masaoka-Koga staging of thymomas with current modifications added by the International Thymic Malignancy Interest Group (ITMIG) indicated by the asterisk (*)

Stage	Definition
Stage I	Grossly and microscopically completely encapsulated tumor. * This includes tumors with invasion into but not through the capsule or tumors in which the capsule is missing but without invasion into surrounding tissues
Stage II	
IIa	Microscopic transcapsular invasion. * Microscopic transcapsular invasion (not grossly appreciated)
IIb	Macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent to but not breaking through mediastinal pleura or pericardium * Gross visual tumor extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), or * Adherence to pleura or pericardium making removal of these structures necessary during resection, with microscopic confirmation of perithymic invasion (but without microscopic extension into or through the mediastinal pleura or into the fibrous layer of the pericardium).
Stage III	Macroscopic invasion into neighboring organ (i.e. pericardium, great vessel or lung) * This includes extension of the primary tumor to any of the following tissues: * Microscopic involvement of mediastinal pleura (either partial or penetrating the elastin layer); or * Microscopic involvement of the pericardium (either partial in the fibrous layer or penetrating through to the serosal layer); or * Microscopically confirmed direct penetration into the outer elastin layer of the visceral pleura or into the lung parenchyma; or * Invasion into the phrenic or vagus nerves (microscopically confirmed, adherence alone is not sufficient); or * Invasion into or penetration through major vascular structures (microscopically confirmed); * Adherence (i.e., fibrous attachment) of the lung or adjacent organs only if there is mediastinal pleural or pericardial invasion (microscopically confirmed)
Stage IV	
IVa	Pleural or pericardial metastases * Microscopically confirmed nodules, separate from the primary tumor, involving the visceral or parietal pleural surfaces, or the pericardial or epicardial surfaces
IVb	Lymphogenous or hematogenous metastasis * Any nodal involvement (e.g., anterior mediastinal, intrathoracic, low/anterior cervical nodes, any other extrathoracic nodes) * Distant metastases (i.e., extrathoracic and outside the cervical perithymic region) or pulmonary parenchymal nodules (not a pleural implant)

Scorsetti et al. (2016)

et al. 2011). However, patients with more advanced thymomas may require more extensive resections, including sterno-thoracotomy, pleurectomy, partial or total pneumonectomy, or pericardiectomy (Scorsetti et al. 2016). The mean resectability rates for stage I, II, III, and IV thymomas are 100%, 85%, 47%, and 26%, respectively (Detterbeck and Parsons 2004). For unresectable thymomas, patients can be treated with neoadjuvant radiotherapy or chemotherapy in order to reduce tumor burden. Neoadjuvant radiotherapy has been reported to increase the rates of complete resection for stage III thymoma to 53–75% (Akaogi et al. 1996). Neoadjuvant radiotherapy is generally given concurrently with platinum-based chemotherapy. Alternatively, induction chemotherapy followed by surgery and adjuvant ChemoRT can be used in the management of thymomas (Venuta et al. 1997; Kim et al. 2004; Lucchi et al. 2005).

The role of adjuvant radiation therapy in the management of thymomas remains controversial. Because of the rarity of thymomas, there are no Phase III randomized trials that provide concrete data on the indications for radiation therapy in thymoma patients. The recurrence rate for stage I thymoma is approximately 3%, occurring at a mean interval of 10 years following surgical resection, and postoperative radiation therapy is not indicated for stage I thymomas (Scorsetti et al. 2016). Postoperative radiotherapy for stage I thymomas has no significant effect on recurrence or overall survival (Zhang et al. 1999).

Adjuvant radiotherapy is commonly administered to patients with stage III–IVA thymoma or those with an incomplete surgical resection (Scorsetti et al. 2016). This practice of delivering adjuvant radiotherapy following incomplete resection is based on small retrospective studies (Curran et al. 1988; Ciernik et al. 1994). The 1988 study by Curran et al. included 103 thymoma patients, 28 of which underwent biopsy or subtotal resection for stage III disease (Curran et al. 1988). Of these 28 patients, 20 underwent postoperative radiotherapy and 9 of 20 developed either local or distant recurrence. Ciernik et al. reported the survival rates of 31 stage III or IV thymoma patients receiving postoperative radiation therapy at doses ranging from 42 to 66 Gy, with 10-year overall survival being 57% and 8% for stage III and IV disease, respectively (Ciernik et al. 1994).

Outcomes of adjuvant radiotherapy following complete surgical resection have been reported in several studies, with mixed results. In a Japanese study, Haniuda et al. evaluated the recurrence rate of thymoma patients treated with complete tumor resection followed by adjuvant radiotherapy to 40–50 Gy. In this study, there was a significant improvement in local recurrence in patients with thymomas macroscopically adherent to the pleura that were treated with postoperative radiotherapy compared to those not treated with postoperative radiotherapy (0% vs. 36.4%, $p < 0.05$). However, postoperative radiotherapy did not significantly affect local recurrence in thymoma patients with microscopic pleural or pericardial invasion (Haniuda et al. 1996). Chen et al. showed no significant difference in disease-free survival or overall survival in stage II thymoma patients treated with or without postoperative radiotherapy. It was reported that histologic type B3 stage II thymomas have significantly worse disease-free survival compared to the other thymoma histologies (60.8% vs. 92.3% at 10 years, $p = 0.001$) (Chen et al. 2010). In a 2016 retrospective study from the Chinese Alliance for Research in Thymomas (ChART), overall survival and disease-free survival were actually worse in stage I–III thymoma patients who underwent complete resection and adjuvant radiotherapy compared to surgical resection alone. However, the ChART study showed improved overall and disease-free survival in patients with incomplete resections who received postoperative radiotherapy compared to those who were treated with surgery alone (Liu et al. 2016). In contrast to the ChART study, the meta-analysis by Zhou et al. showed improved overall survival in stage II and III thymoma patients treated with complete surgical resection and postoperative radiotherapy compared to surgery alone (Zhou et al. 2016).

Radiation doses for thymoma depend on the extent of resection. The general practice is to treat with 45–50 Gy for negative or close (<1 mm) margins, 54–60 Gy for microscopically positive

resection margins, and 60–70 Gy for gross residual disease or as definitive treatment (Komaki and Gomez 2014). Thymic carcinomas are often treated more aggressively with higher adjuvant radiation doses with or without concurrent chemotherapy (Yano et al. 1993; Ogawa et al. 2002; Hsu et al. 2002). Studies have shown adjuvant radiotherapy to improve disease-free survival with a trend toward improved overall survival (Yano et al. 1993; Hsu et al. 2002; Mao and Wu 2015).

In the neoadjuvant or definitive setting, the radiation field should cover the entire extent of disease as visualized on CT or PET imaging. In the adjuvant setting, any pretreatment scans should be fused to the CT simulation planning scan to cover the surgical bed and preoperative tumor volume. Elective nodes are generally not covered in the treatment volume. Four-dimensional CT (4D CT) should be used to improve target localization, and patients should undergo simulation in the supine position with their arms above their heads (Gomez and Komaki 2010; Gomez et al. 2011). Radiotherapy should be delivered by 3D conformal technique or IMRT to reduce the dose to the surrounding normal tissues. Because of its characteristic Bragg peak, proton beam radiation therapy can further reduce dose to normal structures. In a prospective study of 27 thymoma patients treated with proton beam therapy, no patient experienced grade ≥3 toxicity, and 3-year regional control and overall survival were 96% and 94%, respectively (Vogel et al. 2016).

Thymomas are uncommon tumors that are primarily managed surgically, though neoadjuvant or adjuvant radiotherapy can improve local control and is preferentially recommended for patients with stage III/IV tumors or those that are incompletely resected.

3 Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is a rare malignancy arising from the coelomic cavities of the body, including the pleura, peritoneum, pericardium, and tunica vaginalis (van Meerbeeck et al. 2011; Chen and Pace 2012). The vast majority of MPM occur in the pleura, with approximately 80% of MPM occurring in the visceral pleura and 20% occurring in the parietal pleura (van Meerbeeck et al. 2011; Chen and Pace 2012; Zhang et al. 2015). The median age at diagnosis is 72–74 years (Chen and Pace 2012). There are approximately 2,000–3,000 new cases of MPM in the United States annually, and about 80% of MPM patients are men (Chen and Pace 2012; Price and Ware 2009; Taioli et al. 2014). The incidence of MPM peaked in the early 1990s in the United States (Price and Ware 2009; Taioli et al. 2014). The predilection of men for MPM and the declining incidence are related to asbestos exposure and the subsequent asbestos ban.

Approximately 60% of patients with MPM present with dyspnea and chest wall pain (van Meerbeeck et al. 2011; Chen and Pace 2012; Robinson et al. 2005). Dyspnea is most commonly due to accumulation of pleural fluid in the thoracic cavity, and chest wall pain is due to invasion into the thoracic wall (van Meerbeeck et al. 2011). Patients can have phrenic nerve paralysis and concomitant impaired diaphragmatic movement (van Meerbeeck et al. 2011; Zhang et al. 2015). Other presenting symptoms include weight loss, fatigue, cough, chest wall pain, pneumothorax, and cardiac tamponade (van Meerbeeck et al. 2011; Chen and Pace 2012).

CT imaging generally reveals thickening of the pleura often with pleural plaques and calcifications (van Meerbeeck et al. 2011; Chen and Pace 2012; Zhang et al. 2015). MRI may be used preoperatively to assess for invasion into the chest wall or diaphragm (Zhang et al. 2015). Biopsy is generally performed via thoracoscopy (van Meerbeeck et al. 2011; Rodriguez 2015). The three most common histologic subtypes of MPM in the order of decreasing frequency are epithelial, biphasic, and sarcomatoid (Chen and Pace 2012; Zhang et al. 2015). Biphasic MPM consists of a combination of epithelial and sarcomatoid cells (Chen and Pace 2012).

The prognosis of MPM is dismal, with median overall survival (without treatment) ranging from 4 to 12 months (van Meerbeeck et al. 2011;

Zhang et al. 2015; Taioli et al. 2014; Flores et al. 2010). SEER data indicates a 5-year overall survival of approximately 9% (Chen and Pace 2012). MPM patients with epithelial histology have the most favorable prognosis, while patients with sarcomatoid histology have the worst prognosis (Herndon et al. 1998; Ray and Kindler 2009). Female gender, better performance status, and lower white blood cell count have been associated with improved survival (Chen and Pace 2012; Price and Ware 2009).

Optimal management of stage I–III medically operable MPM consists of either resection followed by sequential chemotherapy ± hemithoracic radiotherapy or neoadjuvant chemotherapy followed by surgical resection ± hemithoracic radiotherapy (de Perrot et al. 2009; Krug et al. 2009; Bolukbas et al. 2011; Thieke et al. 2015). Surgical resection consists of either extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D); mediastinal nodal dissection is recommended with either procedure (Rice et al. 2011). EPP consists of removal of the involved pleura, lung, ipsilateral diaphragm, and pericardium. P/D consists of resection of the involved pleura and all gross tumor as a lung-sparing surgery. An extended P/D involves a total pleurectomy and resection of the diaphragm and pericardium. In many cases of MPM, a complete resection is not possible with either EPP or P/D (Hasani et al. 2009; Friedberg 2013). A meta-analysis by Cao et al. comparing extended P/D to EPP showed significantly lower perioperative mortality (2.9% vs. 6.8%, $p = 0.02$) and morbidity (27.9% vs. 62.0%, $p < 0.0001$) with extended P/D (Cao et al. 2014). Additionally, there was a trend toward improved median overall survival with P/D vs. EPP (13–29 months vs. 12–22 months, respectively) (Cao et al. 2014). Even among patients with early-stage MPM, there is a higher postoperative complication rate and worse long-term quality of life following EPP compared to P/D (Rena and Casadio 2012). Therefore, EPP tends to only be recommended on clinical trials and/or at specialized, high-volume surgical centers (van Zandwijk et al. 2013).

Chemotherapy alone may be recommended for patients with medically inoperable or metastatic MPM (Kelly et al. 2011; Blomberg et al. 2015). The preferred chemotherapy regimen used either alone or as a component of multimodality therapy is cisplatin/pemetrexed (Kondola et al. 2016). In a Phase III randomized trial in MPM patients who were not surgical candidates, cisplatin/pemetrexed significantly increased median survival compared to cisplatin alone (12.1 vs. 9.3 months, $p = 0.02$) (Vogelzang et al. 2003). In a multicenter randomized Phase III trial in patients with unresectable MPM, bevacizumab plus cisplatin/pemetrexed significantly improved median overall survival compared to cisplatin/pemetrexed alone (18.8 vs. 16.1 months, $p = 0.016$) (Zalcman et al. 2016).

Outside of a clinical trial, radiotherapy alone or in combination with chemotherapy is not recommended for MPM, as radiotherapy alone results in significant morbidity with no improvement in survival (McAleer et al. 2009). Historically, prophylactic radiotherapy has been administered to instrument insertion sites to prevent tumor seeding (Low et al. 1995; De Ruysscher and Slotman 2003). Boutin et al. showed significantly decreased local failure in MPM patients receiving 21 Gy in three fractions using 12.5–15 MeV electrons within 15 days of an invasive procedure compared to patients who did not receive radiotherapy (0% vs. 40%, $p < 0.001$) (Boutin et al. 1995). In contrast, a 2007 study using the same dose-fractionation regimen (with either photons or electrons) following a pleural invasive procedure showed no significant difference in local failure (O'Rourke et al. 2007). Both of the aforementioned trials were limited with small numbers of patients. In order to assess the utility of prophylactic irradiation to intervention sites, an ongoing multicenter Phase III trial in the United Kingdom plans to enroll 374 MPM patients to receive either 21 Gy in three fractions or no radiotherapy directed at instrumentation sites (Bayman et al. 2016).

Local failure after surgical resection of early MPM ranges from 30% to 60% (McAleer et al. 2009). Therefore, adjuvant radiotherapy may be administered after EPP or P/D. Several prospective studies have evaluated the outcomes of adjuvant radiotherapy following EPP (Yajnik et al.

2003; Flores et al. 2006; Pagan et al. 2006; Rea et al. 2007; Batirel et al. 2008; Tonoli et al. 2011). The recommended adjuvant dose after EPP is 45–54 Gy for negative margins or 54–60 Gy for positive margins. In a study from Memorial Sloan-Kettering Cancer Center, 54 MPM patients received adjuvant EBRT 3–5 weeks after EPP. A total dose of 54 Gy was administered via anterior and posterior fields in 30 daily fractions of 1.8 Gy with spinal cord blocks after 41.4 Gy. Liver, heart, and stomach blocks were all added, and the pleural/diaphragm dose in these blocked regions was supplemented with electrons. Median overall survival was 33.8 months for stage I and II patients and 10 months for stage III and IV patients. Radiotherapy was well tolerated, with most toxicities being of grades 1 and 2 (Rusch et al. 2001).

IMRT has also been used to deliver adjuvant radiotherapy following EPP in an effort to improve dose conformality to the target volume and decrease dose to normal structures (Chi et al. 2011). The clinical target volume (CTV) is usually defined as all surgically violated areas and clips, including the thoracic wall, diaphragm, pleural reflections, deep margin of the incision, and ipsilateral mediastinal nodes (Tonoli et al. 2011; Ahamad et al. 2003). In a study from MD Anderson Cancer Center, 86 patients who received EPP for MPM underwent adjuvant IMRT. The CTV dose was 45–50 Gy, with a boost to 55–60 Gy for areas at high risk for recurrence or positive margins. Median survival and 1-year survival were 14.6 months and 55%, respectively. There were five patients who experienced treatment-related death due to pulmonary toxicity (Gomez et al. 2013b). In an Italian study from 2011, 50 MPM patients received IMRT after EPP. The dose was 45–50 Gy in 25 fractions given to the affected hemithorax and ipsilateral mediastinum. A simultaneous integrated boost to 60 Gy was given to sites of involved margins. Three-year overall survival and disease-free survival rates were 57% and 60%, respectively (Tonoli et al. 2011). In a 2016 study of 62 MPM patients, hypofractionated IMRT of 25 Gy in five daily fractions delivered 6–8 days prior to EPP showed median overall and disease-free survivals of 51 months and 47 months, respectively (de Perrot et al. 2016). However, 39% of the patients developed grade 3 or higher complications (de Perrot et al. 2016).

More modern series report on the use of adjuvant radiotherapy following P/D and chemotherapy with reasonable results and acceptable toxicity. These studies report median survival of 23.3–28.4 months and grade ≥3 pulmonary toxicity rates of 8–20% (Rosenzweig et al. 2012; Patel et al. 2012; Chance et al. 2015). The largest study by Minatel et al. reported on 69 patients treated with either extended P/D or partial pleurectomy followed by chemotherapy and postoperative IMRT. The IMRT dose was 50 Gy in 25 fractions with a boost to 60 Gy in 30 fractions for areas at risk for residual disease. Two-year locoregional control was 65% and 64%, and overall survival was 65% and 58% with extended P/D and partial pleurectomy, respectively (Minatel et al. 2015).

Palliative radiotherapy can be used to treat chest wall pain from MPM with doses of 20–40 Gy in fractions of 4 Gy (Macleod et al. 2014; Taioli et al. 2015). Several retrospective and Phase II studies evaluating palliative radiotherapy for pain control in pleural MPM have been published (Bissett et al. 1991; Davis et al. 1994; de Graaf-Strukowska et al. 1999; El Hossieny et al. 2010; Jenkins et al. 2011). de Graaf-Strukowska et al. reported improved pain relief with a median dose of 36 Gy in 4 Gy per fraction compared to a median dose of 30 Gy in 2 Gy per fraction (de Graaf-Strukowska et al. 1999).

MPM is a devastating disease with a poor prognosis. The mainstay of treatment is surgery for resectable disease and chemotherapy for unresectable or metastatic disease. Adjuvant radiotherapy following EPP or P/D can be delivered for patients who have responded favorably to surgery and chemotherapy though it should preferably be performed on a clinical trial and/or at high-volume centers.

Conclusion

There are numerous areas of controversy regarding the treatment of lung cancer and uncommon thoracic malignancies like thymoma and MPM. Ongoing clinical trials will hopefully provide answers to several of these

controversies. Much work is still needed to develop clinical studies, novel therapeutics, and biomarker-driven therapies to improve the outcomes for our patients.

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Soft Tissue Sarcomas of the Extremities

Christie Binder and Arthur Y. Hung

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Abstract

Soft tissue sarcomas are highly diverse mesenchymal malignancies of muscle, peripheral nerves, and adipose or fibrous connective tissues. Sarcoma classification had been entirely based on resemblance to various tissue types. More recently, classifications have been revised to include molecular features and genetic profiles of sarcoma. While our treatment paradigms for soft tissue sarcomas were developed on, what we know now to be oversimplified, histologic classifications, the addition of specific karyotyping and biomarkers has not changed our overall approach to these tumors in the majority. The local therapy paradigms are still based on surgery and radiation for the vast majority of these tumors.

1 Adjuvant Radiation Therapy or Observation

One of the major controversies in the management of soft tissue sarcoma is which population of sarcoma patients should be offered adjuvant radiation. The original randomized controlled trials demonstrating the benefit of adjuvant radiation in local control included patients with low- and high-grade sarcomas.

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While surgery is the mainstay of treatment for soft tissue sarcomas (STS) of the extremity, a radical resection by amputation causes morbidity that can be avoided by more conservative limb-sparing surgeries (LSS). An improvement in toxicity, however, is only useful if efficacy is not lost. Two National Cancer Institute (NCI) trials prospectively randomized patients to explore LSS with adjuvant radiation treatment. In the first trial, 43 patients with STS of the extremity without clinical evidence of nodal or metastatic disease were randomized 1:2 to amputation or LSS plus postoperative radiation. Radiation was 1.8–2 Gy fractions to 45–50 Gy to at-risk areas and 60–70 Gy to the tumor bed. Four LSS patients had positive margins. All patients in both arms received postoperative chemotherapy with Doxorubicin, Cyclophosphamide, and high-dose Methotrexate. Most patients had Grade 3 disease in the lower extremities. No statistically significant difference was found between the two arms for 5-year disease-free survival (71% LSS vs. 78%) or overall survival (83% LSS vs. 88%). While LSS had 4 local recurrences, amputation had none ($p = 0.06$). Distant recurrence developed in 3 out of 16 patients who had amputations and 2 out of the 27 who had LSS. Thus, for high-grade soft tissue sarcomas, LSS plus adjuvant RT with chemotherapy was not statistically different from amputation with chemotherapy at 5 years but does trend toward a higher local recurrence rate. The increase in local recurrence did not affect overall survival or distant disease. Though this trial is limited by its small sample size, it was the first prospective randomized trial to establish the non-inferiority of LSS plus radiation (Rosenberg et al. 1982).

The second pivotal prospective randomized NCI trial compared LSS with or without postoperative radiation for high-grade (Grades 2–3) and low-grade STS of the extremity (Grade 1 and benign). Ninety-one high-grade tumors were randomized 1:1 to LSS with chemotherapy (Doxorubicin and Cyclophosphamide) with or without postoperative radiation (45 Gy in 1.8 Gy fractions to at-risk areas and 63 Gy to the tumor bed). Fifty low-grade tumors were randomized and treated similarly but without chemotherapy. At 10 years, adjuvant radiation reduced local recurrence in all cases but did not affect distant metastases or overall survival. High-grade tumors treated without radiation had 9 local recurrences, but tumors that received radiation had none. Distance metastases occurred in 25–35% of patients at 10 years, and overall survival was about 75%. Low-grade tumors treated without radiation had 8 local recurrences in 10 years, and tumors treated with radiation had 1 local recurrence. Each arm had 2 distant recurrences. Overall quality of life scores were similar for patients treated with or without radiation at 3 years, but patients treated with radiation reported decreased joint motion, increased edema, and weakness in treated areas. Edema and weakness improved with time. More than 2/3 of tumors were in the lower extremity. This follow-up NCI study demonstrated a reduction in local recurrence with adjuvant radiation for all tumor grades but no overall survival benefit for any tumor grade. Given the normal tissue toxicities, the likelihood of recurrence and morbidity from salvage surgery should be considered when evaluating the benefit of adjuvant radiation. [REF YANG] Twenty-year follow-up of this study continued to show no difference in overall survival but an improvement in local control. Limb edema, functional deficits, and wound complications were not statistically different between the groups. These results have to be interpreted with caution as only 54 patients could be reached for follow-up and tumors of all grades were analyzed together (Beane et al. 2014).

The question of whether adjuvant brachytherapy could substitute for external beam was addressed in a prospective randomized trial of extremity and superficial trunk STS and published initially in 1996. This trial from Memorial Sloan-Kettering Cancer Center randomized patients who underwent a gross total resection to brachytherapy (Ir-192 interstitial 42–45 Gy over 4–6 days to cavity and 2 cm margin) or no adjuvant radiation. Patients deemed at a high risk for distant metastases were offered chemotherapy at the discretion of the treating physician, and mostly patients with high-grade tumors were given the option. Brachytherapy improved 5-year local control for

high-grade tumors (89% vs. 66%, $p = 0.0025$) but not low-grade tumors ($p = 0.49$). No difference in 5-year freedom from distant metastases or disease-specific survival was seen regardless of tumor grade. Combined analysis of all grades revealed a 5-year freedom from distant metastases of 83% with brachytherapy vs. 76% without ($p = 0.65$); 5-year disease-specific survival was 84% with brachytherapy and 81% without ($p = 0.65$). Wound complications over 3 years were more frequent when catheters were loaded prior to 6 days postoperatively (Pisters et al. 1996). Based on data from this trial, adjuvant brachytherapy benefits patients with high-grade soft tissue sarcomas in order to improve local control.

In general, we recommend adjuvant radiation for all high-grade tumors. Because of the low risk of metastatic disease developing, for low-grade tumors we share the decision-making with the patient and our multi-disciplinary colleagues about the ramifications of adjuvant radiation vs. recurrence and re-resection.

2 Preoperative Versus Postoperative Radiation Therapy

After establishment of LSS and adjuvant radiation as an acceptable definitive therapy for non-metastatic STS of the extremity, timing of adjuvant treatment became a matter of debate. Retrospective data guided our decision-making until data from a landmark randomized controlled trial was available.

A retrospective study out of M.D. Anderson reviewed 517 cases to compare effectiveness of pre- vs. postoperative radiation. Extremity, head and neck, and trunk STS were included. Preoperative radiation was given 4–6 weeks before LSS and averaged 50 Gy in 25 fractions. Postoperative radiation was given 4–8 weeks after surgery and averaged 60–70 Gy in 30–35 fractions. Patients with large or high-grade tumors were offered chemotherapy at the discretion of the treating physician. After multivariate analysis, the study concluded that the timing of radiation did not affect survival outcomes. Overall 10-year local control was 78%, freedom from nodal relapse was 96%, freedom from distant metastases was 61%, and disease-specific survival was 59%. Ten-year complications (soft tissue necrosis, osteoradionecrosis, bone fracture, bone necrosis, edema, and fibrosis) were significantly higher with postoperative radiation (9% vs. 5%, $p = 0.03$) (Zagars et al. 2003).

The prospective clinical trial from Princess Margaret Hospital examined differences in treatment toxicity based on radiation timing. The trial randomized patients with STS of the extremity to preoperative radiation to the tumor (50 Gy in 25 fractions with 5 cm margins distally and proximally) followed by LSS 3–6 weeks later or surgery followed by postoperative radiation to the resection cavity 3–6 weeks later (50 Gy with 5 cm margins distally and proximally and 16–20 Gy boost to the resection cavity and gross disease plus a 2 cm margin). If preoperative cases had positive margins, then a 16–20 Gy boost to the resection cavity and gross disease plus a 2 cm margin was given. Most tumors were grade 3. The primary endpoint, wound complication at 120 days, was seen in 35% of preoperative patients and 17% of postoperative patients ($p = 0.01$). Only 1 case of upper extremity wound complication was observed. All other cases were seen in the lower extremity, particularly the thigh. Large tumor size (>10 cm) also correlated with wound complications. More grade 2 skin toxicity was seen in postoperative radiation (O'Sullivan et al. 2002). Quality of life metrics such as the Musculoskeletal Tumor Society Rating Scale, the Toronto Extremity Salvage Score, and the Short Form-36 favored postoperative radiation at 6 weeks but showed no difference from 3 to 24 months (Davis et al. 2002). At 2-year follow-up, postoperative radiation trended toward greater fibrosis (48% vs. 31%), stiffness (23% vs. 18%), and edema (23% vs. 15%). The differences were not statistically significant; however, 129 patients were included in this analysis and the trial was not powered to detect differences in these secondary endpoints (Davis et al. 2005). At 2.5 years, overall survival slightly favored preoperative radiation ($p = 0.0481$), but this study was not powered for survival outcomes (O'Sullivan et al. 2002).

Taken together, the above studies do not show a difference in survival outcomes between pre- and postoperative radiation. Preoperative radiation to the lower extremity is more prone to wound complications, but postoperative radiation is more likely to cause edema, joint stiffness, and fibrosis. The increased late toxicity of postoperative radiation is at least partially attributable to the higher dose and larger field size after resection.

Given that the limb function and quality of life measures favor preoperative radiation, at our institution, we recommend preoperative radiation for all patients with upper extremity tumors. For lower extremity tumors, we have a discussion with the orthopedic oncologists regarding the likelihood and ramifications of wound complications for each individual patient's situation. We will also discuss our radiation techniques and adjust where possible, for instance to spare tissue based on the likely surgical approach and closure plan. Ultimately, the orthopedic oncologist makes the decision about the timing of the surgery and radiation.

3 Chemotherapy

The question of whether adjuvant chemotherapy is beneficial is still under debate for non-Ewings family STS. Due to the heterogeneity of STS in general and the infrequent presentation of any one subtype, it is difficult to conduct large clinical trials for individual histologies.

A study by the Sarcoma Meta-analysis Collaboration (SMAC) published in 1997 reviewed prospective randomized trials accrued before 1997. Eligible trials included patients treated for resectable STS, adults, and localized disease and included chemotherapy and no chemotherapy arms. Fourteen trials were identified (Sarcoma Meta-analysis Collaboration 1997). This meta-analysis was updated in 2008 and included the SMAC trials and four new trials meeting eligibility criteria published between 1997 and April 2007. The update performed subset analysis of trials based on chemotherapy—doxorubicin-based or doxorubicin and ifosfamide (Table 1). When all trials were combined, a statistically significant benefit in local recurrence, distant recurrence, and overall survival was found. However, subgroup analysis showed no benefit for local recurrence for either group or for overall survival using doxorubicin-based chemotherapy without ifosfamide. It is difficult to directly apply these results to the clinic as the study does not report absolute benefits, though they do report number needed to treat. Additionally, it was not possible to parse out tumor grade or histology. Thus, while chemotherapy demonstrated an overall benefit for all localized STS patients, specifically who it would most benefit is still under study. Although this article did not comment on toxicity, chemotherapies carry a high side effect profile. Ideally in the future, subgroups will be identified such that fewer patients will be needed to treat to see a benefit (Pervaiz et al. 2008).

The most recent systematic review and meta-analysis evaluated the benefit of multi-agent chemotherapy for advanced STS (Zer et al. 2018). Twenty-two prospective trials that randomized to single agent or multi-agent chemotherapy were included. All of the trials were published between 1974 and April 2016. Overall, multi-agent chemotherapy had a marginal benefit for overall sur-

Table 1 Relative risks (RR), 95% confidence intervals (CI), *p*-value (*p*), and number needed to treat (NNT) for local recurrence, distant recurrence, and overall survival

	RR	Local recurrence			RR	Distant recurrence			RR	Overall survival		
Treatment		95% CI	*p*	NNT		95% CI	*p*	NNT		95% CI	*p*	NNT
All	0.73	0.56–0.94	0.02	25	0.67	0.56–0.82	0.0001	12	0.77	0.64–0.93	0.01	17
Doxorubicin	0.75	0.56–1.01	0.055		0.69	0.56–0.86	0.001		0.84	0.68–1.03	0.09	
Doxorubicin and Ifosfamide	0.66	0.39–1.12	0.12		0.61	0.41–0.92	0.02		0.56	0.36–0.85	0.01	

vival (HR 0.79, $p = 0.02$) and progression-free survival (HR 0.86, $p = 0.05$). Results were not statistically significantly different between trials with anthracycline controls vs. non-anthracycline controls.

The use of multi-agent chemotherapy for advanced disease rather than single agent therapy seems to have a statistically significant but marginal improvement in survival outcomes. Outside of dedicated sarcoma centers, many centers do not have routine experience with the multi-agent regiments typically used for soft tissue sarcomas. Ideally future investigations will be able to identify which histologies benefit and potentially improving the therapeutic ratio.

4 Volumes

Radiation oncologists have investigated what the ideal treatment volumes for STS since LSS and radiation were found to be an acceptable alternative to amputation. Initially, clinical treatment volumes (CTVs) included entire muscle compartments, and the uncertainty of daily setup in extremities led to large margins as well. However, improved treatment planning, targeting, and image guidance have allowed a reduction in volumes without a loss of efficacy, thereby decreasing radiation toxicity.

A 2010 RTOG consensus meeting established guidelines for preoperative radiation treatment volumes for large (>5 cm) intermediate and high-grade extremity STS. The gross target volume (GTV) was defined as gross tumor as seen on a T1-weighted contrast-enhanced MRI fused with the simulation CT. The CTV encompassed the GTV + a 3 cm margin proximally and distally, a 1.5 cm margin radially, and clinically suspicious edema as seen on a T2-weighted MRI. Volumes were trimmed based on anatomic barriers and compartments (Wang et al. 2011).

A reduced treatment volume has been supported by studies examining the location of local recurrences. For example, a Princess Margaret Hospital retrospective review of 768 patients treated with LSS and radiation found that most local recurrences occurred within the treatment field. Preoperative planning treatment volumes (PTV) encompassed the GTV with a 5 cm longitudinal and 1–2 cm radial margin. 50 Gy in 2 Gy fractions was delivered. Positive margins in preoperative radiation cases received an additional 10–16 Gy to the original gross disease and a 2 cm margin. For cases with postoperative radiation, the PTV included the resection cavity, a 5 cm circumferential margin, the surgical scar, and drainage sites for the first 50 Gy and a 2 cm margin around the original gross disease for the last 10–16 Gy. Local recurrences were defined as in field, marginal, or out of field. With an average of 12 years of follow-up, the recurrence rate was 6.4% in field, 0.3% marginal, and 1.1% out of field. Larger treatment volumes would not have decreased the local recurrence rate as most recurrences received full dose in the PTV. Other factors intrinsic to the tumor itself most likely have a greater influence on recurrence (Dickie et al. 2012).

RTOG 0630 investigated whether reduced treatment volumes in conjunction with IMRT would be acceptable. This multi-institutional Phase II study examined late toxicity and setup error for extremity STS treated with preoperative radiation with daily image guidance. GTV was as defined by the 2010 consensus meeting (T1 contrast-enhanced MRI), but CTV varied based on tumor size and grade. For high- and intermediate-grade tumors ≥8 cm, the CTV included the GTV, 3 cm proximally and distally, 1.5 cm radially, and suspicious edema as seen on a T2-weighted MRI. For low-grade tumors or tumors <8 cm, CTV longitudinal margins were decreased to 2 cm, and the radial margin was decreased to 1 cm. The PTV was the CTV with a 5 mm margin. At 3.6-year follow-up, 5 of 79 patients had a local recurrence, and all local recurrences were in field. Late toxicities ≥ Grade 2 occurred in 10.5% of patients at 2 years as compared to 37% in the phase III National Cancer Institute of Canada SR2 trial (O'Sullivan et al. 2002; Davis et al. 2005; Wang et al. 2015).

RTOG 0630 also tracked shifts and rotations based on daily image guidance. Right/left and anterior/posterior errors were greatest. Setup errors as large as 2 cm were recorded. Overall, it

was estimated that without daily image guidance, a PTV margin of 1.5 cm would be required. Images were aligned to bony anatomy nearest the PTV and included at least one joint (Li et al. 2016).

While RTOG 0630 was only a phase II study, in combination with the data from Princess Margaret showing the majority of local failures occurring in-field, we have elected to adopt the treatment volume definitions from RTOG 0630 with the caveat that even if we are not using IMRT, we continue to use daily image-guidance to reduce setup error.

5 Conclusion

Currently, our treatment for soft tissue sarcomas has slowly evolved over the last 3 decades with refinements in surgical and radiation techniques. We currently treat a heterogenous group of cancers in identical fashion. In the future, our therapeutic strategies will hopefully require identification of key molecular drivers of the different subtypes that will enable us to target our therapies more effectively.

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Radiotherapy in the Management of Prostate Cancer

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Abstract

Prostate cancer remains one of the most common cancer diagnoses among men in North America. The majority are treated with surgery or radiotherapy; and the advent of technological precision has driven remarkable improvements in clinical outcomes. Here, we highlight existing controversies surrounding the use of radiotherapy in the management of prostate cancer, with specific focus on different clinical scenarios.

1 Background

Each year, 1.1 million men are diagnosed with prostate cancer (CaP) worldwide. Based on documented global incidence patterns, the diagnosis of CaP is more common in the Western part of the world, contributed in part by the advocacy of routine prostate-

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specific antigen (PSA) screening in men, despite the lack of supportive evidence (Potosky et al. 1995). Inadvertently, this has led to an increase in the number of patients receiving definitive treatment for organ-confined CaP, along with concerns of overtreatment in some of these men (Welch and Albertsen 2009; Cooperberg et al. 2010; Mitchell 2013).

A well-established mechanism for stratifying patients who are diagnosed with CaP involves assessing PSA, Gleason score (GS) and primary tumour extent (T category) (D'Amico et al. 1998) and classifying patients into low- , intermediate- or high-risk categories based on these clinical and pathological indices. Nonetheless, significant inter-patient heterogeneity exists within each risk category, and recent NCCN guidelines have been updated to include additional very low- and very high-risk categories to address this issue (Mohler et al. 2014). For the majority of indolent localised CaP, treatment options include radical prostatectomy (RadP), radiotherapy (RT) and active surveillance (intended for patients with low-risk disease) (Wilt et al. 2012). High-quality retrospective evidence have suggested equivalence in terms of tumour control and toxicities between RadP and RT, but this remains a debatable issue given the paucity of level I randomised evidence (D'Amico et al. 1998; Grimm et al. 2012; Resnick et al. 2013; Sooriakumaran et al. 2014).

Regarding the choice of RT technique, external beam treatment and brachytherapy are proven alternatives (D'Amico et al. 1998; Koukourakis et al. 2009; Peinemann et al. 2011). Brachytherapy modalities include low-dose rate (LDR) monotherapy (permanent radioactive iodine seed (I^{125}) insertion) or interstitial implant insertion for remote afterloading high-dose rate (HDR) boost following external beam RT (Galalae et al. 2004; Martinez et al. 2002, 2011; Hoskin et al. 2012; Morton et al. 2011). With regard to external beam treatment, there are, at present, a variety of options with intensity-modulated RT (IMRT), image-guided RT (IGRT), proton RT and stereotactic body RT (SBRT). These technological advances offer precise irradiation of the prostate gland, leading to significant reduction in late RT-induced adverse events (Sheets et al. 2012). Nonetheless, while clinical outcomes of CaP patients following RT have been mostly favourable, several issues covering various aspects of treatment remain widely debated. Among these are arguments pertaining to elective pelvic nodal irradiation, the use of dose escalation and hypofractionation and the choice of patients for RT as opposed to RadP and vice versa. In this chapter, we shall review and discuss the prevailing controversies in the RT management of CaP.

2 The Role of Radiotherapy in PSA Screening-Detected Prostate Cancer

Evidence from two large PSA screening trials have both highlighted the significant health burdens associated with overdiagnosis (Schröder et al. 2009, 2012, 2014; Andriole et al. 2009, 2012; Heijnsdijk et al. 2012). While the North American PLCO study failed to demonstrate a mortality reduction in men who have been subjected to PSA screening, the companion European ERSPC study was positive in demonstrating that numbers needed to screen to avoid one CaP death continue to fall over time (Schröder et al. 2014). Nonetheless, there is also recognition that PSA is a 'poorly' predictive test for CaP, due to its intrinsic high false positivity. For example, between 10 and 70% of men across the different study sites in ERSPC had a positive PSA test, but a negative pathological diagnosis. It is very likely that complementation with other non-invasive measures such as multiparametric MRI or urine prostate cancer antigen 3 (PCA3) is required to enhance the value of PSA screening, and these strategies await testing.

In the same period, two other randomised trials were conducted to query if upfront RadP conferred a survival benefit over watchful waiting in patients with organ-confined CaP (Bill-Axelson et al. 2011, 2014; Wilt et al. 2012). Similar to the PSA screening studies, conflicting results were reported. In the Swedish study by Axelson et al. (SPCG-4), early surgery was associated with a reduction in CaP deaths, with the largest benefit being observed in patients harbouring intermediate-risk disease (Bill-Axelson et al. 2011, 2014). Conversely, in the trial by Wilt et al. (PIVOT), no difference in survival outcomes was observed between early surgical intervention and

observation, except in patients with a presenting PSA of >10 ng/ml (Wilt et al. 2012). A key disparity between the trials, which could perhaps explain the contrast in results, relates to the time period when these studies were initiated. Unlike SPCG-4 that commenced prior to the PSA screening era, the majority of patients from PIVOT had been PSA screened, which is in keeping with the observation of less advanced disease, corresponding to fewer cancer deaths in the latter trial (proportion of T1c tumours was 12%, SPCG-4 vs. 50%, PIVOT; CaP-specific mortality was 19.6% vs. 7.1%, respectively).

Currently, there is a massive effort by the UK study group to address (1) the role of PSA screening (CAP) and (2) active surveillance against either RadP or RT in the management of PSA screening-detected CaP (ProtecT) (Lane et al. 2010, 2014). Results of the latter trial should be available in 2016. Until then, it may not be unreasonable to extrapolate evidence from the surgical-based studies to the RT patient, if we were to assume equipoise between RT and RadP. Treatment-related mortality is unquestionably low with RT. Rather, in the majority of men who have been treated for CaP, competing non-CaP causes of deaths are not negligible (Roobol and Bokhorst 2014). As evidenced in the PIVOT trial, only a mere 52 patients (7.1%) died from CaP compared to 354 (48.4%) deaths from all other causes (Wilt et al. 2012). It is thus pertinent in contemporary clinical practice to consider factors such as expected life expectancy and patient's expectations prior to consenting them for treatment. Development of methods to identify non-indolent CaP is also important to ensure treatment is not inappropriately withheld. In this regard, multiparametric MRI and molecular tumour profiling are promising potential approaches (van den Bergh et al. 2014; Lalonde et al. 2014).

3 Dose Escalation in Localised Prostate Cancer

The earliest work supporting a dose-response above 60 Gy in localised CaP included published reports by Zelefsky et al. (1998). In their prospectively collected series, planned radiation doses to the entire prostate gland were gradually increased from 64.8 to 81.0 Gy, and a dose-response relationship was established for both PSA nadir and control, with the most striking effect being observed in intermediate- and high-risk disease. Other benefits of dose escalation that have been demonstrated subsequently include reduction of local relapses, distant metastases and CaP-specific mortality (PCSM) (Zelefsky et al. 2011; Kuban et al. 2011).

There are now several large randomised trials that have investigated the implications to survival and toxicities with dose escalation. Mature results of these studies are summarised in Table 1. Pollack et al. conducted a trial of 78 vs. 70 Gy and observed superior biochemical control and a reduced likelihood of distant relapses and CaP deaths with 78 Gy. In a subgroup analysis, those <70 years of age and PSA of >10 ng/ml benefited most from the higher dose (Pollack et al. 2000, 2002; Kuban et al. 2008, 2011). The improvement in biochemical control is consistent across all studies, with reported gains of 10–25% (Al-Mamgani et al. 2008; Heemsbergen et al. 2014; Zietman et al. 2010; Beckendorf et al. 2011; Dearnaley et al. 2014; Michalski et al. 2014, 2015).

Nonetheless, the strongest argument against dose escalation in localised CaP points to the blatant fact that none of the studies demonstrated an associated overall survival (OS) advantage. In the most recent report of RTOG 0126, where nearly 1,500 men with intermediate-risk CaP were randomised to 79.2 vs. 70.2 Gy, a 7-year OS was comparable between both cohorts (HR 0.98 [0.79–1.21]) (Michalski et al. 2014, 2015). This, despite significant improvements across all other clinical endpoints (including reduction of distant metastasis) with dose escalation in RTOG 0126. Again, competing causes of death significantly confounded the potential benefit of PCSM reduction with dose escalation (3%, PCSM, vs. 19.8%, other competing causes). Thus, it is clear that prudent selection of patients for dose escalation is required. A nice example for this is provided by Kuban et al. where they demonstrated in their post-hoc analysis of the MD Anderson trial that benefits of dose escalation were limited to high-risk patients who are <70 years old (Kuban et al. 2011). Another analysis of 1,060 men from

Table 1 Overview of main characteristics and findings of radiotherapy dose-escalation trials for localised prostate cancer

Trial	Start	*N*	Patients	RT dose levels	ADT	Median follow-up	Main finding (control group vs. dose-escalated group)	Toxicity (control group vs. dose-escalated group)	Publication
MRC RT01 (UK)	1998	843	IR: 37% HR: 43%	64 Gy in 32 fractions vs. 74 Gy in 37 fractions	All pts received neoadjuvant ADT for 3–6 months	10 years	10-year BPFS 43% vs. 55%, ($p = 0.0003$) 10-year OS 71% for both groups ($p = 0.96$)	5-year late GU grade ≥ 2 8% vs. 11% ($p = 0.056$) Late GI grade ≥ 2 24% vs. 33% ($p = 0.055$)	Dearnaley et. al. 2007, 2014
MDACC 93-002	1993	301	IR: 46% HR: 34%	70 Gy in 35 fractions vs. 78 Gy in 39 fractions	No	8.7 years	8-year FFBF 59% vs. 78% ($p = 0.004$) 8-year FFDM 95% vs. 99%, ($p = 0.059$) 8-year OS 78% vs. 79%, ($p = 0.315$)	Late GI grade ≥ 2 13% vs. 26%, ($p = 0.013$) Late GU grade ≥ 2 8% vs. 13%, (p = NS)	Pollack et. al. 2002 Kuban et. al. 2008
PROG 95-09	1996	393	LR:58% IR: 37% HR: 5%	70.2 GyE in 39 fractions vs. 79.2 GyE in 44 fractions (proton boost)	No	8.9 years	HR 0.57 for local failure in dose-escalation group 10-year BFR 32.0% vs. 17.4% ($p = 0.0001$) 10-year OS 78.4% vs. 83.4% ($p = 0.41$)	Late GU grade ≥ 3 2% Late GI grade ≥ 3 1% (both groups, p = NS)	Zietman et. al. 2010
Dutch trial (CKTO 6910)	1997	664	IR: 27% HR: 55%	68 Gy in 34 fractions vs. 78 Gy in 39 fractions	Yes, 22% of pts	9.2 years	BFR 46% vs. 52% ($p = 0.025$) CFR 34% vs. 37% ($p = 0.4$) PCD 13% vs. 13% ($p = 0.8$) OS 31% vs. 30% ($p = 0.9$)	7-year late GU grade ≥ 2 40% vs. 41% ($p = 0.6$) Late GI grade ≥ 2 25% vs. 35% ($p = 0.04$)	Al-Mamgani et. al. 2008 Heemsbergen et. al. 2014

Trial	Start	*N*	Patients	RT dose levels	ADT	Median follow-up	Main finding (control group vs. dose-escalated group)	Toxicity (control group vs. dose-escalated group)	Publication
RTOG 0126	2002	1,532	70% had PSA < 10 ng/ml, 84% with GS 7, 57% had T1 disease	70.2 Gy in 39 fractions vs. 79.2 Gy in 44 fractions	No	7 years	10-year OS 66% vs. 67% ($p = 0.87$) BFR 43% vs. 26% ($p < 0.0001$) LPR 8% vs. 4% ($p = 0.0059$) DMR 8% vs. 5% ($p = 0.026$) STR 21% vs. 13.5% ($p = 0.0002$)	Late GU/GI grade ≥ 2 37% vs. 45% ($p = 0.0012$) Time to late GI grade ≥ 3 was higher for the 79.2 Gy arm ($p = 0.035$) but time to late GU grade ≥ 3 toxicity was not ($p = 0.14$)	Michalski et. al. 2015
GETUG 06	1999	306	HR: 29%	70 Gy in 35 fractions vs. 80 Gy in 40 fractions	No	5 years	BRR 39% vs. 28% ($p = 0.036$)	Late GU grade ≥ 2 10% vs. 17.5% ($p = 0.046$) Late GI grade ≥ 2 14% vs. 19.5% ($p = 0.22$)	Beckendorf et. al. 2011

ADT androgen deprivation therapy, *MRC* Medical Research Council, *IR* intermediate risk, *HR* high risk, *BPFS* biochemical progression-free survival, *OS* overall survival, *GU* genitourinary, *GI* gastrointestinal, *MDACC* MD Anderson Cancer Centre, *FFBF* freedom from biochemical failure, *FFDM* freedom from distant metastasis, *NS* not significant, *GyE* Grey Equivalent, *HR* hazard ratio, *BFR* biochemical failure rate, *BFR* biochemical failure rate, *CFR* clinical failure rate, *PCD* prostate cancer death, *PSA* prostate-specific antigen, *GS* Gleason score, *LPR* local progression rate, *DMR* distant metastasis rate, *STR* salvage therapy rate, *BRR* biochemical relapse rate

British Columbia also suggested that better biochemical control post-RT was only associated with prolonged survival in individuals with ≥10-year life expectancy (Herbert et al. 2012).

Moreover, dose escalation is not without risks, as evidenced by the increased likelihood of late adverse effects to the rectum and bladder. Fortunately, severe (RTOG grade 3) late effects were not always more frequent. Modern technologies like IMRT and IGRT are also useful tools in mitigating risks of late toxicities imposed by dose escalation (Al-Mamgani et al. 2009; Sheets et al. 2012; Michalski et al. 2013).

Going forward, an improved schema of selecting patients for dose escalation is desperately needed. An example would be dichotomising intermediate-risk patients into favourable and unfavourable subgroups using additional pathological indices (percentage of core positivity and a predominant GS 4 pattern) and testing if this manner of stratification predicts for better outcomes with dose escalation (Zumsteg et al. 2013).

This issue of dose escalation is further complicated by the synergistic effects of androgen deprivation and RT. It is generally agreed that combination androgen deprivation is synonymous with a dose-escalation effect. Several randomised studies of combined modality treatment have confirmed this hypothesis (Bolla et al. 2002; D'Amico et al. 2004; Denham et al. 2005; Lawton et al. 2007; Horwitz et al. 2008; Jones et al. 2011), but we still lack information on the optimal RT dose in the setting of combined treatment. The UK-led MRC RT01 study reported a subgroup analysis where high-risk patients had a better biochemical relapse-free rate (bRFR) with RT of 74 Gy vs. 70 Gy in combination with 6 months of androgen deprivation, but no impact on OS was observed (Dearnaley et al. 2014). EORTC 22991 and the Quebec study formally test both parameters in a 2 × 3- (70 Gy vs. 74 Gy vs. 78 Gy, with or without 6 months of androgen deprivation) and 2 × 2- (70 Gy vs. 76 Gy, with or without 6 months of androgen deprivation) study design, respectively (Bolla et al. 2014; Nabid et al. 2015). Results of these studies will inform on the optimal strategy, as well as provide scientific insights into the molecular interactions between androgen deprivation and RT.

4 RT Versus Radical Prostatectomy in High-Risk Prostate Cancer

There is limited evidence to conclude if RT or RadP ought to be the treatment of choice in men with high-risk CaP. Retrospective evidence may suggest equipoise between them in terms of survival and preventing clinical progression, but proponents of RadP often argue on the grounds of detailed pathological staging and accurate prognostication (Boorjian et al. 2011; Parikh and Sher 2012). The potential of a decreased likelihood of distant metastasis with RadP has also been suggested (Porter et al. 2006; Zelefsky et al. 2010). A recent meta-analysis comparing RadP and RT had included 19 retrospective studies with differing levels of confounding biases and drew the conclusion that RT is associated with a poorer OS and a higher rate of PCSM compared to RadP (Wallis et al. 2015). It should however be cautioned that nearly every retrospective study comparing RadP vs. RT in the treatment of CaP is inherently weakened by open or hidden biases that may not be easily managed by any statistical means, including propensity score matching.

Nonetheless, on the backbone of recent evidence generated by several randomised trials, the current standard regime for high-risk CaP patients treated with RT involves combined androgen deprivation (Bolla et al. 2002; D'Amico et al. 2004; Denham et al. 2005; Lawton et al. 2007; Horwitz et al. 2008; Jones et al. 2011). The consensus also agrees that optimal duration of androgen deprivation is between 18 and 36 months for high-risk patients (Nabid et al. 2013; Bolla et al. 2009; Horwitz et al. 2008; Zapatero et al. 2015). In patients who are already on long-term androgen deprivation, irradiation of the prostate confers a twofold reduction in CaP deaths and an estimated 8–15% improvement in OS, persisting even after 8 years (Widmark et al. 2009; Warde et al. 2011; Mason et al. 2015). A recent meta-analysis confirmed the efficacy of combined modality therapy against either single-modality hormonal therapy or RT (Schmidt-Hansen et al. 2014). Thus, the prevailing dilemma remains determining the right patients for RadP or combination hormonal RT. A fine illustrative example is a 65-year-old healthy man who is diagnosed with low volume, cT2a

(peripheral zone tumour on MRI), PSA 15 ng/ml, but GS 9 (on targeted biopsy), and intraductal carcinoma-associated CaP, for which either option can be resoundingly argued for and against.

5 Elective Whole Pelvis Radiotherapy in Node-Negative Disease

Although the indication for prostate RT is definitive in patients harbouring localised high-risk disease, the same cannot be said for prophylactic irradiation of the pelvic lymph nodes. To date, three randomised trials (RTOG 77-06, 94-13, GETUG-01) have examined if irradiating the pelvic lymph nodes conferred OS or bRFR benefits in CaP, none of which yielding any positive findings (Asbell et al. 1988, 1998; Roach et al. 2003; Pommier et al. 2007) (Table 2). In reality, the strongest evidence supporting the role of empirical pelvic irradiation comes solely from several retrospective series (Seaward et al. 1998a, b; Pan et al. 2002; Jacob et al. 2005; Aizer et al. 2009; Milecki et al. 2009; Mantini et al. 2011).

RTOG 77-06 was the first of three trials, conducted prior to the implementation of PSA screening and D'Amico risk stratification. Briefly, patients with node-negative organ-confined CaP, ascertained by radiology or surgical staging, were randomised to receive prostate RT with or without whole pelvis RT. OS was comparable between both arms, even after a long follow-up duration of 12 years (Asbell et al. 1998). However, a significant proportion of the study participants (approximately 80%) had favourable GS, which would have portended for a low risk of nodal metastasis, thus raising the question if pelvic RT should have been indicated in the first place.

RTOG 94-13 was a more contemporary study designed to address two key issues simultaneously. Apart from testing the hypothesis that pelvic RT improves progression-free survival (PFS) in patients with CaP, it also examined the impact of neoadjuvant vs. adjuvant sequencing of androgen deprivation. Rather appropriately as opposed to RTOG 77-06, patient selection was performed based on a ≥15% risk of nodal metastasis estimated using the Roach's equation (Roach et al. 1994). In the initial report, patients who were randomised to whole pelvis RT (WPRT) and neoadjuvant hormonal therapy (NAHT) experienced an improved 4-year PFS compared to the other treatment arms (60% vs. 44%, prostate only RT (PORT) and NAHT; vs. 49%, WPRT and adjuvant hormonal therapy (AHT); vs. 50% PORT and AHT) (Roach et al. 2003). However, this difference diminished with longer follow-up. Even more odd, men who received WPRT and AHT fared the worst among the four subgroups (Lawton et al. 2007). Ultimately, the study was not powered for cross comparisons between the four treatment arms, thus allowing little room for interpretation of the actual value of WPRT. Around the same time, the French trialists' group reported the early 5-year results of GETUG-01, which just like the other preceding studies, also failed to justify WPRT (Pommier et al. 2007). It is also apparent that patient selection was inconsistent across the three trials. Although GETUG-01 comprised of mostly patients with NCCN-defined high-risk CaP (78.7%), only approximately half of the study cohort possessed a ≥15% risk of lymph node metastasis as estimated by the Roach's equation (48.7% and 43.2% in WPRT and PORT arms, respectively).

Retrospective series however offered a different perspective to the benefits of irradiating the pelvic lymph nodes (Seaward et al. 1998a, b; Pan et al. 2002; Jacob et al. 2005; Aizer et al. 2009; Milecki et al. 2009; Mantini et al. 2011). Seaward et al. retrospectively selected patients who were at risk of lymph node metastasis using the Roach's equation and demonstrated that these patients experienced an improved PFS if they received WPRT (Roach's score ≥ 15–35%, median PFS 39.5 months for WPRT vs. 22.5 months for PORT; >35%, 27.2 months vs. 20.8 months, respectively) (Seaward et al. 1998a, b). Pan et al. also presented similar findings using a different method of lymph node risk stratification (Partin's) (Partin et al. 2001; Pan et al. 2002). In that study, WPRT was only beneficial in individuals with an intermediate risk of lymph node metastasis, but not for low- and high-risk patients. Nonetheless, the main limitation of both studies relates to the fact that the majority of patients were not treated with concomitant androgen deprivation and RT.

A number of predictive models for lymph node metastasis have been developed (Partin et al. 1993;

Table 2 Overview of trials addressing the issue of pelvic nodal radiotherapy

Trial	Start	*N*	Inclusion criteria	Randomisation	Median follow-up	Main finding	Toxicity	Publication
RTOG 77-06 (Pre-PSA era)	1978	445	Stage A2 and B without clinical (lymphangiogram) or biopsy evidence of lymph node involvement	65 Gy in 1.8–2 Gy fractions to prostate alone vs. pelvic node irradiation to 45 Gy with a boost of 20 Gy to the prostate	7 and 12 years	7-year OS 80% vs. 78% RFS 88% vs. 90% MFS 84% vs. 83% NED 67% vs. 64% (all p = NS) 12-year OS difference (p = NS)	Not reported	Asbell et. al. 1988 Asbell et. al. 1998
RTOG 9413	1995	1,323	All T and all GS PSA < 100 ng/mL Risk of nodal involvement > 15%	70.2 Gy to the prostate alone vs. 50.4 Gy to the pelvis + 19.8 Gy boost to the prostate Neoadjuvant + concurrent + adjuvant HT vs. adjuvant HT	7 years	OS and PFS difference between WPRT and PORT group was NS	No difference in late GU grade ≥ 3 (p = 0.16) Late GI grade ≥ 3 5% (WPRT + NHT arm) vs. 1% (PORT + NHT) (p = 0.002)	Roach et. al. 2003 Lawton et. al. 2007

GETUG 01	1998	444	T1b–T3, N0 6 months of ADT allowed for HR patients	46 Gy to the pelvis followed by boost to the prostate to 66–70 Gy vs. 66–70 Gy to the prostate alone	3.5 years	5-year PFS 66% vs. 65.3% ($p = 0.34$)	Acute GU grade ≥ 3 was significantly higher in the prostate-only radiotherapy arm. Pelvic irradiation was associated with a small but NS increase in late GU grade ≥ 2	Pommier et. al. 2007
RTOG 0924 (active trial)	2011	Target accrual 2,580 Current accrual 1,068	GS 7–10 + T1c-T2b + PSA < 50 ng/ml GS 6 + T2c-T4 or ≥50% positive biopsies + PSA < 50 ng/ml GS 6 + T1c-T2b + PSA > 20 ng/ml	Neoadjuvant ADT + prostate and seminal vesicle RT (45 Gy) + boost to prostate and proximal seminal vesicles (IMRT 34.2 Gy or brachy) vs. Neoadjuvant ADT + whole-pelvic RT (45 Gy) + boost to prostate and proximal seminal vesicles (IMRT 34.2 Gy or brachy)	N/A	N/A	N/A	Recruitment ongoing

OS overall survival, *RFS* recurrence-free survival, *MFS* metastasis-free survival, *NED* no evidence of disease, *NS* not significant, *T* T stage, *PSA* prostate-specific antigen, *GS* Gleason score, *HT* hormonal therapy, *PFS* progression-free survival, *WPRT* whole pelvis radiotherapy, *PORT* prostate only radiotherapy, *NHT* neoadjuvant hormonal therapy, *ADT* androgen deprivation therapy, *HR* high risk

Roach et al. 1994; Nguyen et al. 2009; Briganti et al. 2012a, b). While most have been validated to some extent in large surgical series, Roach's equation is perhaps the most intuitive and routinely applied formula. It also outperforms other newly proposed models (Yu and Nguyen formulas) and remained valid in the extended pelvic lymph node dissection (ePLND) series (Abdollah et al. 2013). Based on data generated from ePLND series, it can be surmised that risks of pelvic lymph node metastasis are in the range of 5–6%, 20–25% and 30–40% for low- , intermediate- and high-risk CaP, respectively (Heidenreich et al. 2007). There is further suggestion that extent of lymph node dissection correlated with PCSM (Joslyn and Konety 2006). It is thus counter-intuitive if radiation oncologists avoid pelvic RT in patients with intermediate- and high-risk CaP. Perhaps, a way forward is to independently test the value of WPRT/ePLND in subgroups of CaP patients stratified according to their likelihood of nodal metastasis. Along similar principles, RTOG 0924 is a randomised phase III trial evaluating WPRT and androgen deprivation in patients with 'favourable' high-risk CaP (defined as GS 7–10, PSA < 50 ng/ml; GS 6, PSA < 50 ng/ml, cT2c-4; GS 6, PSA > 20 ng/ml, cT1c-2b) (Kattan et al. 2003).

6 Whole Pelvis Radiotherapy in Node-Positive Advanced Prostate Cancer

Conventional thinking among oncologists suggests that node-positive CaP is associated with adverse prognosis and is likely incurable. This is backed by robust observations in surgically treated cohorts that nodal metastasis was a strong determinant of distant metastasis and PCSM (Gerber et al. 1997; Cheng et al. 2001; Eggener et al. 2011). However, there is now emerging evidence that node-positive CaP represents a heterogeneous subgroup, with a substantial proportion of men capable of experiencing long-term bRFR and survival with aggressive treatment (Cheng et al. 2001; Swanson et al. 2006; Briganti et al. 2009; von Bodman et al. 2010; Carlsson et al. 2013; Touijer et al. 2014; Abdollah et al. 2014). Consistent in all the published reports, the number of involved nodes is a significant prognostic determinant, independent of other clinical indices like GS, PSA and cT category. Men who have limited nodal metastases of ≤2 nodes are less likely to fail biochemically, develop distant metastasis and encounter PCSM (Cheng et al. 2001; von Bodman et al. 2010; Touijer et al. 2014). In fact, 75–86% of 10-/15-year cancer-specific survival rates post-RadP and ePLND have been reported in patients with ≤2 pathologically involved lymph nodes (Boorjian et al. 2007; Briganti et al. 2008; Schumacher et al. 2008; Touijer et al. 2014; Gakis et al. 2014). Going a step further, long-term survival has been reported in men with node-positive CaP managed by RadP and PLND alone, despite evidence presented by Messing et al. favouring immediate over delayed androgen deprivation in this group of men (Messing et al. 2006; Schumacher et al. 2008; Touijer et al. 2014). Collectively, these findings argue for the role of aggressive treatment in carefully selected men with node-positive CaP. In support, three surgical series, including a series by Engel et al. comprising of 957 patients, have independently reported a two-fold PFS benefit with combined local and hormonal treatment than with hormonal treatment alone (Engel et al. 2010; Grimm et al. 2002; Steuber et al. 2011).

Likewise, there is also emerging evidence demonstrating the efficacy of RT in node-positive CaP. Based on data queried from the National Cancer Data Base (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) database, Tward et al. and Rusthoven et al. have independently reported PCSM and OS benefits with offering RT to these high-risk patients (Tward et al. 2013; Rusthoven et al. 2014). Tward et al. reported an HR of 0.66 for PCSM with pelvic RT in their analysis of 1,100 patients, while Rusthoven et al. demonstrated an absolute benefit of 20% for OS with either RadP or RT. A similar degree of benefit was also observed with combined modality treatment as opposed to hormonal therapy alone in the subgroup of men with pathologically proven node-positive CaP from RTOG 85-31 (Lawton et al. 2005). RTOG 96-08 (a phase III trial of total androgen suppression vs. total androgen suppression plus definitive external beam irradiation for pathologic lymph node-positive adenocarcinoma of the prostate) closed

prematurely due to poor accrual, but, nonetheless, reported a 20% benefit in 10-year OS in men who received combination treatment (46% vs. 67%) (Zagars et al. 2001). Two other more recent analyses, namely, an exploratory analysis of the STAMPEDE trial (NCT00268476; MRC PR08; CRUK/06/019) and a retrospective review of 3,682 NCDB records of men with node-positive CaP by Lin et al., also indicated better failure-free survival (HR = 0.45) and OS (24.4% absolute improvement) with the addition of local treatment (James et al. 2015a, b; Lin et al. 2015).

Overall, there is sound non-level 1 evidence to support the argument that pelvic RT should be offered to patients with node-positive CaP. Nonetheless, unresolved issues in this regard include target and dose definitions for RT planning and patient selection. There are now consensuses on the coverage of pelvic nodal chains for clinical target volume contouring (Taylor et al. 2007; Lawton et al. 2009). Although there is uncertainty regarding the optimal dose to gross nodal metastasis, high tumouricidal doses (≥70 Gy) to sites in the pelvis that historically would have been unachievable using 3D conformal RT are now possible with IMRT and IGRT. Separately, we lack an optimal criterion for recommending pelvic RT to patients with node-positive disease. To this end, Abdollah et al. recently published a novel PCSM-risk stratification model based on 1,107 patients with pathologically positive nodes who underwent RadP, ePLND and androgen deprivation with or without pelvic RT (Abdollah et al. 2014). They determined that two categories of men with node-positive CaP were likely to benefit from adjuvant RT: (1) ≤2 positive nodes, GS 7–10 and pT3b/4 or positive surgical margins and (2) 3–4 positive nodes. This represents the first of its kind clinical decision-making tool and should certainly be validated prospectively.

7 Oligometastatic Prostate Cancer: Radiotherapy for Palliation or Cure?

The concept of 'curing' patients with oligometastatic disease across all tumour types has gained popularity once again in recent times. While the evidence in support of a 'curable' oligometastatic state is more abundant in some cancer types like colorectal cancer, renal cell carcinoma and sarcomas, it is conceivable that a subset of patients with metastatic CaP can be 'cured' with aggressive treatment. Current methods of stratifying for these favourable patients are imprecise and do not incorporate indices indicative of tumour biology. For the lack of a better measure, patients with metastatic CaP are often crudely stratified based on (1) number of extra-pelvic lesions, (2) whether these metastatic tumour sites are amendable to ablative therapies (surgery or SBRT), and (3) the magnitude of PSA response following initial androgen deprivation. In truth, it is not yet known if patients harbouring these characteristics indeed have a better prognosis, but a few retrospective reviews have suggested a benefit in disease control with aggressive therapy. For example, Culp et al. reviewed 374 men with metastatic CaP from the SEER database who underwent RadP or brachytherapy and reported better OS and failure-free survival for individuals who underwent local treatment compared to those who did not (Culp et al. 2014). In another report of 119 patients who were treated with SBRT to isolated nodal or skeletal metastasis, 3-year progression-free rate was 31%, with corresponding 95% of 3-year and 88% of 5-year OS in that cohort (Ost et al. 2016). Although these results may seem promising at first glance, several questions still exist on the clinical management of this patient subgroup.

Foremost, the ideal clinical endpoint that constitutes a robust surrogate for the assessment of treatment efficacy is unclear. In this instance, suitable choices include clinical PFS, OS, time to salvage hormonal therapy or time to castrate resistance. Perhaps, for the purpose of a clinical trial, it may be prudent to select an endpoint that is both measurable at an early time-point and also functions as a good surrogate for long-term outcome, especially since a substantial proportion of patients with metastatic CaP treated in the docetaxel era do survive beyond 5 years (James et al. 2015a, b). Secondly, much work is needed in defining the optimal treatment schema. Uncertainties pertaining to (1) timing of RT post-initial androgen deprivation, (2) RT doses to the prostate and metastatic lesions, (3) duration of androgen deprivation (2–3 years vs. continuous lifelong) and (4) combination strategies

with docetaxel ought to be examined. Hopefully, an ongoing Canadian prospective trial (ClinicalTrials.gov; NCT02563691) will provide answers to some of these conundrums. Thirdly, through multiregion deep whole genome sequencing of multifocal primary and recurrent CaP, we now have a deeper understanding of the clonal dynamics and divergent evolutionary processes driving the progression to lethal CaP (Hong et al. 2015; Gundem et al. 2015). We need to learn how best to incorporate biological and clinical indices to enable better patient stratification, so that we truly select for the 'curable' oligometastatic CaP patients. Research across these domains is desperately needed, but meanwhile the treatment paradigm of metastatic CaP continues to evolve rapidly.

8 Adjuvant Radiotherapy or Salvage Only at Biochemical Failure Post-Radical Prostatectomy?

It is estimated that following RadP, approximately 30–60% of men will require RT as salvage for biochemical failure (Pfister et al. 2014). Likelihood of salvage is dependent on clinical indices, such as pre-RT PSA, GS, surgical margin status and PSA doubling time (Stephenson et al. 2007). Individually, these parameters are indicative of tumour burden, biology and likelihood of local vs. distant recurrences.

While there is cognition of RT as an effective salvage measure for biochemical relapse post-RadP, the timing of treatment is debatable. The argument for offering RT immediately post-RadP in a select group of high-risk patients (pT3/4 and/or with positive surgical margin) relates closely to the correlation between tumour control probability (TCP) and microscopic tumour burden. Three randomised trials were performed to test this hypothesis. Overview of these landmark trials is presented in Table 3. SWOG 8794 was the first conducted between 1988 and 1997 recruiting 425 CaP patients harbouring such features. Updated results after a median follow-up of 12 years revealed that men who received adjuvant RT experienced a lower incidence of distant metastases compared to those who were observed (9.3% vs. 17.5%, respectively; HR = 0.71 [0.54–0.94]) (Thompson et al. 2009). OS, bRFR and dependence on salvage hormonal therapy also favoured adjuvant RT (Thompson et al. 2006). EORTC 22911 studied the role of adjuvant RT in 1,005 men and reported a 50% relative reduction in 10-year risks of biochemical and local relapses (Bolla et al. 2005, 2012). Incidences of distant failures however did not differ between treatment arms in EORTC 22911. To note, incidence of distant metastasis was also significantly lower in EORTC 22911 relative to SWOG 8794 (7.2% vs. 17.5%). This discrepancy is unexplained by differences in clinical characteristics between the studies (higher proportion of pT3b, but lower GS tumours in SWOG 8794 than EORTC 22911). Last but not least, the German study group (ARO 96-02) showed, like the other two studies, a relative reduction of 50% in biochemical recurrence with adjuvant RT in patients who achieved an undetectable PSA post-RadP (about a third of patients had a PSA of >0.2 ng/ml post-RadP in SWOG 8794 and EORTC 22911) (Wiegel et al. 2009, 2014). Again, no benefit in terms of distant metastasis control and OS was observed in ARO 96-02.

Perhaps, the inter-study variation for incidences of distant metastasis (13.4% of SWOG 8794 vs. 7.2% of EORTC 22911 vs. 15.3% of ARO 96-02) highlights the fact that clinical indices alone are imprecise for prediction of lethal disease in the adjuvant setting. In this regard, genomic indices could be a powerful tool (Antonarakis et al. 2012; Viers et al. 2014; Den et al. 2014; Evans et al. 2016). Using a novel RNA-based genomic classifier, Den et al. were able to stratify for patients at risk of rapid failures post-RadP and would benefit from early rather than late RT, potentially providing the first biomarker as a clinical decision-making tool for timing of RT post-RadP (Den et al. 2015). Evans et al. also demonstrated the prognostic utility of a DNA damage and repair pathway-based gene expression signature for distant metastasis post-RadP in a large sample size of 1,090 men, validated by multi-cohort testing (Evans et al. 2016). Separately, the indolent nature of CaP also

Table 3 Basic characteristics of landmark adjuvant radiotherapy trials

Trial	Start	*N*	Inclusion criteria	RT dose	PSA at trial entry	Median follow-up	Definition of PSA failure	Main finding	Toxicity	Publication
SWOG 8794	1988	425	pT3 or R1	60–64 Gy to the prostate bed	≥0.2 ng/mL: 33% <0.2 ng/mL: 66%	10.6 years	PSA > 0.4 ng/mL	MFS 12.9 years vs. 14.7 years for observation vs. ART ($p = 0.016$) OS 13.3 years vs. 15.2 years for observation vs ART ($p = 0.0023$)	Proctitis 3.3% vs. 0% Urethral strictures 17.8% vs. 9.5% Urinary incontinence 6.% vs. 2.8% (ART vs. observation)	Thompson et. al. 2006 Thompson et. al. 2009
EORTC 22911	1992	1,005	pT2-3 and/or R1	60 Gy to the prostate bed	>0.2 ng/mL: 30% ≤0.2 ng/mL: 70%	10.6 years	Increase in PSA > 0.2 µg/L over the lowest post-op value	10-year BPFS 61% vs. 41% for ART vs. observation ($p < 0{\cdot}0001$)	10-year incidence - all grade 3 5.3% vs. 2.5% GU grade 2 21.3% vs. 13.5% GI grade 2 2.5% vs. 1.9% (ART vs. observation)	Bolla et. al. 2005 Bolla et. al. 2012
ARO 96-02	1996	388	pT3-4 ± R1	60 Gy	Undetectable	10 years	Two increasing PSA readings	10-year PFS 56% vs. 35% (ART vs. WS) ($p < 0.0001$)	Grade 3 bladder toxicity 1% vs. 0% (ART vs. WS)	Wiegel et. al. 2009 Wiegel et. al. 2014

SWOG Southwest Oncology Group, *PSA* prostate-specific antigen, *R1* positive margins, *MFS* metastasis-free survival, *ART* adjuvant radiotherapy, *OS* overall survival, *EORTC* European Organisation for Research and Treatment of Cancer, *BPFS* biochemical progression-free survival, *GU* genitourinary, *GI* gastrointestinal, *PFS* progression-free survival, *WS* wait and see

implies that time from biochemical progression to clinical disease is often protracted. In a large-scale analysis of 1997 men who underwent RadP, median time taken to develop distant metastasis from the point of biochemical failure was 8 years (Pound et al. 1999). If so, 10 years of follow-up may be inadequate for the assessment of distant metastasis-related outcomes in adjuvant vs. salvage RT trials.

In light of the results of SWOG 8794, EORTC 22911 and ARO 96-02, adjuvant RT is currently jointly endorsed by ASTRO, AUA and ASCO in patients with (1) extensive pT3a or pT3b and (2) GS 8–10 and (3) those who failed to achieve post-operative PSA nadir (Valicenti et al. 2013; Freedland et al. 2014).

In spite of this, a recent nationwide survey revealed continuous declining use of post-operative RT in CaP from 2005 to 2011 in the United States (Sineshaw et al. 2015). Arguments for this trend include; first, SWOG 8794 and EORTC 22911 had failed to incorporate undetectable PSA as an inclusion criterion, and therefore it is often argued that these patients were at a significantly higher risk of progression and mortality at the outset (Wiegel et al. 2015). Secondly, a subsequent central pathology review of the EORTC 22911 cohort suggested that only patients with positive margins derived a benefit from adjuvant RT (van der Kwast et al. 2007). Thirdly, up to 50% of patients who experienced biochemical failure are salvaged successfully if RT is initiated early enough, as indicated by several large retrospective studies (Trock et al. 2008; Stephenson et al. 2007; Briganti et al. 2012a, b; Pfister et al. 2014). Finally, adjuvant RT is not without increased toxicities (increased incidence of urethral strictures and urinary incontinence) (Bolla et al. 2005; Thompson et al. 2006; Wiegel et al. 2009; Iyengar et al. 2011). Given the ongoing controversy regarding the preferred management of patients with high-risk features on RadP, three large randomised trials, namely, RADICALS (Radiotherapy and Combined Androgen Deprivation after Local Surgery), RAVES (Radiotherapy Adjuvant vs. Early Salvage following Radical Prostatectomy) and GETUG 17 aimed to resolve the issue of timing of RT post-RadP (Parker et al. 2007; Pearse et al. 2014) (Table 4). Primary endpoints of these studies are PCSM, bRFR and event-free survival, respectively. Results of these studies are expected in 2016.

9 Prevailing Controversy of the α/β of Prostate Cancer

Alpha-beta ratio (α/β) is a parameter indicative of tissue fraction size sensitivity and is estimated through the linear quadratic (LQ) equation. Briefly, tissues with low α/β are more sensitive to fraction size changes, and this intrinsic characteristic bears therapeutic implications in terms of designing optimal RT fractionation schemes. In CaP, since the seminal publication by Brenner et al., several subsequent analyses have independently concluded a low α/β ratio (range of 1.2–4.1) for CaP, thus setting the stage for several studies testing a variety of novel hypofractionation schemes (Brenner and Hall 1999; Miralbell et al. 2012; Dasu and Toma-Dasu 2012; Vogelius and Bentzen 2013).

However, despite hypotheses of better outcomes with these hypofractionation schemes that were formulated on the backbone of LQ modelling, evidence so far points only to non-inferiority of hypofractionated RT when compared to conventional RT. Table 5 provides an overview of the results of landmark randomised studies that compared conventional RT against moderately hypofractionated RT schedules (dose/fraction ranging from 2.4 to 3.1 Gy). Early hypofractionation studies by Yeoh et al. and Lukka et al. may have reported better bRFR with hypofractionated treatment schemes, but in truth, the RT doses for the conventional arms were low by contemporary standards (Yeoh et al. 2011; Lukka et al. 2005). Five other large randomised trials, namely, CHHiP, NRG RTOG 0415, Fox Chase Cancer Centre study, Italian study and MD Anderson Cancer Centre study, employed dose-escalated conventional treatment schemes, and early results did not suggest differences in tumour control and toxicities with hypofractionated RT (Dearnaley

Table 4 Ongoing randomised trials comparing adjuvant versus salvage radiotherapy addressing the question of timing of radiotherapy post-radical prostatectomy

Trial	Start	Inclusion criteria	Definition of post-op PSA failure	Randomisation	RT dose	RT volume	ADT	Primary endpoint	Planned accrual
RADICALS (MRC/NCIC) NCT00541047	2007	Post-op PSA ≤0.2 ng/ml and/or pT3/4, GS 7–10, pre-op PSA ≥ 10 ng/ml, R1	Two consecutive rises in PSA and final PSA >0.1 ng/ml or three consecutive rises in PSA	Immediate RT (within 26 weeks after RadP) vs. deferred RT at BF	66 Gy in 33 fr or 52.5 Gy in 20 fr to the prostate bed 46 Gy in 23 fr to the pelvic lymph nodes	Prostate bed ± pelvic lymph nodes	LHRH agonist or bicalutamide 150 mg Randomisation No ADT vs. 6 months vs. 2 years of ADT	DSS	closed; 2840 patients randomized in hormone duration question and 1396 patients randomized in radiotherapy timing question
RAVES (TROG 08.03) NCT00860652	2009	Post-op PSA ≤ 0.1 ng/mL R1, EPE ± pT3b	PSA ≥ 0.2 ng/ml	Adjuvant RT (within 4 months after RadP) vs. early salvage	64 Gy in 32 fr	Prostate bed	Not allowed	BF (PSA ≥0.4 ng/ml)	470 (closed)
GETUG 17 NCT00667069	2007	Post-op PSA ≤ 0.1 ng/mL pT3/4 or R1	PSA > 0.2 ng/ml	Immediate (within 6 months after RadP) vs. delayed RT	66 Gy in 33 fr to the prostate bed 46 Gy in 23 fr to the pelvic lymph nodes	Prostate bed ± pelvic lymph nodes	Triptorelin 6 months	EFS at 5 years	718 (ongoing)

ADT androgen deprivation therapy, *PSA* prostate-specific antigen, *R1* positive margins, *RT* radiotherapy, *RadP* radical prostatectomy, *BF* biochemical failure, *fr* fractions, *GS* Gleason score, *LHRH* luteinising hormone-releasing hormone, *DSS* disease-specific survival, *EPE* extra-prostatic extension *BF* biochemical failure, *EFS* event-free survival

Table 5 Summary of main randomised trials looking at hypofractionated radiotherapy

Trial	*N*	Median follow-up	RT schedule	Gy per fraction	BED (Gy)			Primary outcome	Secondary outcome	Late toxicity	Reference
					α/β = 1.5 (prostate cancer)	α/β = 3 (normal tissue)	α/β = 10 (tumor)				
Australian trial	217	7.5 years	64 Gy/32 fr	2 Gy	149	107	77	7.5-year BRFS 34% ($p < 0.05$)	7.5-year OS 69% (p = NS)	No significant difference	Yeoh et. al. 2006 Yeoh et. al. 2011
			55 Gy/20 fr	2.75 Gy	156	105	70	7.5-year BRFS 53% ($p < 0.05$)	7.5-year OS 71% (p = NS)		
Ontario (Canada)	936	5.7 years	66 Gy/33 fr	2 Gy	154	110	79	5-year BCF 52.95%	5-year OS 85% (p = NS) 2-year PBR 53% (p = NS)	No significant difference	Lukka et. al. 2005
			52.5 Gy/20 fr	2.63 Gy	145	98	66	5-year BCF 59.95%	5-year OS 87% (p = NS) 2-year PBR 51% (p = NS)		
CHHiP (CRUK/06/016)	3,216	5.2 years	60 Gy/20 fr	3 Gy	180	120	78	5-year FFBF 90.6%	Not reported	2-year grade ≥ 2 late GU 1.7% (p = 0.34) 2-year grade ≥ 2 late GI 2.9% (p = 0.1)	Dearnaley et. al. 2016
			57 Gy/19 fr	3 Gy	171	114	74	5-year FFBF 85.9% (p = 0.003)		2-year grade ≥ 2 late GU 1.1% (p = 0.34) 2-year grade ≥ 2 late GI 1.8% (p = 0.1)	
			74 Gy/37 fr	2 Gy	173	123	89	5-year FFBF 88.3%		Not reported	

Trial	*N*	Median follow-up	RT schedule	Gy per fraction	BED (Gy)			Primary outcome	Secondary outcome	Late toxicity	Reference
					α/β = 1.5 (prostate cancer)	α/β = 3 (normal tissue)	α/β = 10 (tumor)				
NRG Oncology RTOG 0415	1,115	5.9 years	73.8 Gy/41 fr	1.8 Gy	162	118	87	7-year DFS 75.6% (p = NS)	FFBF and OS not different	Grade ≥ 3 GI 3% grade ≥ 3 GU 4.5% (both p = NS)	Lee et. al. 2016
			70 Gy/28 fr	2.5 Gy	187	128	88	7-year DFS 81.8% (p = NS)		Grade ≥ 3 GI 4.6% grade ≥ 3 GU 6.4% (both p = NS)	
Fox Chase Cancer Center	303	5.7 years	76 Gy/38 fr	2 Gy	177	127	91	5-year BCDFR 21.4% (p = 0.7)	PCD and OS not different	Grade 3 late GU 3.3% (p = NS) Grade 3 late GI 2% (p = NS)	Pollack et. al. 2013
			70.2 Gy/26 fr	2.7 Gy	197	133	89	5-year BCDFR 23.3% (p = 0.7)		Grade 3 late GU 4% (p = NS) Grade 3 late GI 2% (p = NS)	
Italian	168	5.8 years	80 Gy/40 fr	2 Gy	187	133	96	5-year BFFS 79% (p = 0.065)	5-year FFLF 91% (p = 0.33) 5-year FFDF 86% (p = 0.29) 5-year CSS 82% (p = 0.16) 5-year OS 92% (p = 0.13)	3-year grade ≥ 2 GU 11% 3-year grade ≥ 2 GI 16% (both p = NS)	Arcangeli et. al. 2010, 2012
			62 Gy/20 fr	3.1 Gy	190	126	81	5-year BFFS 85% (p = 0.065)	5-year FFLF 93% (p = 0.33) 5-year FFDF 90% (p = 0.29) 5-year CSS 92% (p = 0.16) 5-year OS 98% (p = 0.13)	3-year grade ≥ 2 GU 14% 3-year grade ≥ 2 GI 17% (both p = NS)	

(continued)

Table 5 (continued)

Trial	*N*	Median follow-up	RT schedule	Gy per fraction	BED (Gy)			Primary outcome	Secondary outcome	Late toxicity	Reference
					α/β = 1.5 (prostate cancer)	α/β = 3 (normal tissue)	α/β = 10 (tumor)				
MDACC	204	5 years	72 Gy/30 fr	2.4 Gy	187	130	89	5-year PSAFFS 96% (p = NS)	Not reported	5-year grade ≥ 2 GU 15.8% (p = 0.97) 3-year grade ≥ 2 GI 10% (p = 0.11)	Kuban et. al. 2008 Hoffman et. al. 2014
			75.6 Gy/42 fr	1.8 Gy	166	121	89	5-year PSAFFS 92% (p = NS)		3-year grade ≥ 2 GU 16.5% (p = 0.97) 3-year grade ≥ 2 GI 5.1% (p = 0.11)	

BED biological equivalent dose, *BRFS* biochemical relapse-free survival, *OS* overall survival, *BCF* biochemical/clinical failure, *PBR* positive biopsy rate, *CRUK* Cancer Research UK, *FFBF* freedom from biochemical failure, *GU* genitourinary, *GI* gastrointestinal, *DFS* disease-free survival, *PCD* prostate cancer death, *OS* overall survival, *NS* not significant, *BCDFR* biochemical and/or clinical disease failure, *BFFS* biochemical failure-free survival, *FFLF* freedom from local failure, *FFDF* freedom from distant failure, *CSS* cancer-specific survival, *MDACC* MD Anderson Cancer Center, *PSAFFS* PSA failure-free survival

et al. 2016; Robert Lee et al. 2016; Pollack et al. 2013; Arcangeli et al. 2012; Kuban et al. 2008). In particular, the fact that bRFR did not differ between treatment arms, despite the design of a more 'biologically effective' RT regime, queries the reliability of the α/β ratio that was applied in some of these studies. For example, in Fox Chase Cancer Centre study by Pollack et al., the experimental hypofractionation arm was estimated to equate to 84.4 Gy in 2 Gy fraction size based on the assumption of an α/β ratio of 1.5 Gy, but yet, no dose-response was observed with the 8.4 Gy dose increment (Pollack et al. 2013). Meanwhile, we await results of two other trials of moderate hypofractionation, namely, the Dutch HYPRO trial of 78 Gy vs. 64.6 Gy in 2 and 3.4 Gy fraction sizes, respectively, and the Ontario PROFIT trial of 78 Gy vs. 60 Gy in 2 and 3 Gy fraction sizes, respectively (Aluwini et al. 2015). With the collection of prospective evidence, it is certain that updated TCP/LQ modelling will yield more robust estimates of the true α/β ratio of CaP.

Taking a step further, studies on extreme hypofractionation have also been conducted in CaP and are gaining popularity in the several parts of the world. Typically, extreme hypofractionation entails a 5-fraction regime with the delivery of 7–7.25 Gy per session using SBRT techniques. There are however concerns that prostate SBRT is associated with an increase of clinically significant urinary and gastrointestinal toxicities (Yu et al. 2014; Kim et al. 2014). Thus, until the preliminary toxicity data of prospective studies becomes available, including the international multicentre PACE trial (Prostate Advances in Comparative Evidence, NCT01584258), this form of treatment should not be routinely offered to patients.

10 The Future of Proton Radiotherapy in the Treatment of Prostate Cancer

Interest in proton particle RT arose from the unique physical characteristics of protons upon tissue interaction. The Bragg's peak, a property associated with particle therapy, describes the deposition of energy at a specific tissue depth with minimal entering and exit doses. The resultant effect is reduced doses to adjacent normal tissues.

The only currently available randomised evidence for the efficacy of proton RT in CaP comes from the Massachusetts General Hospital dose-escalation trial (RTOG 95-09), where study investigators examined the benefits of an escalated boost dose that was delivered using proton RT. Despite a high dose of 79.2 Gy (boost of 28.8 Gy), only 2% and 1% of the cohort experienced late grade ≥ 3 genitourinary and gastrointestinal toxicities, respectively (Zietman et al. 2010). Other studies reporting on comparative effectiveness and patient-reported quality of life outcomes between proton RT and other modalities have been mostly single-institution prospective series (Sheets et al. 2012; Gray et al. 2013; Hoppe et al. 2014; Mendenhall et al. 2014). With limited follow-up, it is preliminary to judge if dosimetric superiority and theoretical advantages of proton RT yield tangible therapeutic benefits, but so far, there appears to be no obvious difference between proton RT and more contemporary techniques of photon RT.

The controversy of utilising proton RT for treating CaP is compounded by the high cost associated with developing these centres (Lawrence and Feng 2013). It is unsurprising then that market-oriented strategies had specifically targeted CaP patients, as opposed to other perhaps more pertinent indications such as brain and eye tumours in children, for the sake of securing financial viability. However, insurance companies have progressively declined to reimburse inflated prices for proton RT in patients with CaP, given the lack of compelling data for a therapeutic advantage. It is thus imperative that the oncology community remained committed to generate sound evidence, preferably from randomised studies, so as to inform on the clinical utility of proton RT in the treatment of CaP (Bekelman and Hahn 2014). To this end, a multi-institutional randomised trial (PARTIQoL, Clinicaltrials.gov, NCT01617161), jointly sponsored by the National Cancer Institute and Massachusetts General Hospital, is currently

underway to compare IMRT and proton RT in the treatment of organ-confined CaP.

Conclusion

The modern practice of IMRT/IGRT in treating CaP has certainly come a long way from less than ideal 3D conformal RT, with patients now enjoying better than ever cure rates and quality of life outcomes due to unparalleled precision in targeting the prostate gland. Having said, judging from the wide-ranging topics that were discussed in this chapter, it is apparent that beyond technology, much work is needed to resolve issues relating to optimal clinical management of CaP. Broadly, they encompassed (1) improving the manner of patient stratification, (2) avoiding unnecessary treatment in patients with favourable prognosis, (3) optimising intensive treatment in patients with unfavourable intermediate-/high-risk/oligometastatic disease and (4) progressive incorporation of technology with biology to achieve greater 'physical' and 'biological' precision in the targeting of CaP. Addressing these issues entails a multidisciplinary approach involving urologists, radiation and medical oncologists and internists; all invested in the endeavour with the sole committed objective of improving the outcomes of patients with CaP.

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Gynecologic Cancers

Kevin Albuquerque, Eric Leung, and Nina A. Mayr

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Abstract

Radiation therapy is a critical component of the multidisciplinary management of gynecologic cancers. In certain organ sites like advanced cervix and vulva/vaginal cancers, it is the primary therapeutic modality and can control tumors while preserving form and function of the affected area. Yet more precise surgical techniques and newer chemotherapeutic and biologic agents have questioned the role of radiation, particularly in light of some of the chronic toxicity it can cause. This chapter highlights the current controversies in the multimodality management of gynecologic cancers. Newer radiation delivery techniques and updated roles for radiation are described for all the subsites of this group in the context of surgical and medical management for these cancers.

1 Introduction

Gynecologic cancers cover a wide spectrum of organs with varying biology and tumor types occurring over a lifetime of a woman. Radiation therapy is a critical component of the multidisciplinary management of most of these tumors. In certain organ sites like advanced cervix and vulva/vaginal cancers, it is the primary therapeutic modality and can control tumors while preserving form and function of the affected area. Continuing clinical research and development of

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new surgical and chemotherapeutic tools have questioned the benefit of adjuvant radiation therapy in uterine and ovarian cancers while cutting-edge stereotactic and intensity-modulated radiation delivery technologies have enabled the use of radiation in previously exempt situations. These areas of progress and controversy are discussed to define the proper place of radiation therapy for gynecologic cancers in this era of personalized medicine

2 Uterine Carcinoma

Endometrial cancer is one of the most common gynecologic malignancies in women worldwide. Standard treatment involves the surgical removal of the uterus, fallopian tubes, and ovaries, with possible lymph node dissection. Radiation therapy has played an important role in the treatment of endometrial cancer in the adjuvant setting; however, despite several large randomized trials evaluating its role, there still exists debate in regard to its efficacy. This section will outline the areas of controversy in the role of radiation for endometrial cancer.

2.1 Early Stage Endometrial Cancer

2.1.1 Randomized Trials

Adjuvant radiation therapy (RT) is a well-established treatment that improves local control in patients with endometrial cancer after surgery. However, several studies including randomized trials have shown no benefit in survival with using this approach (Aalders et al. 1980; Creutzberg et al. 2000; Keys et al. 2004; Group et al. 2009). The *Dutch Gynecology Oncology Group* is currently accruing to the PORTEC-4 study which randomizes patients to two dose schedules of vaginal brachytherapy (7 Gy × 3, 5 Gy × 3) and observation. The rationale for the observation arm is the lack of survival advantage seen in previous studies and the effectiveness of salvage radiation therapy for vaginal recurrences (Creutzberg et al. 2003). Therefore, despite many levels of evidence and randomized data, there remains a wide spectrum of treatment practices in postoperative endometrial cancer, ranging from pelvic radiation, vaginal brachytherapy to observation.

Four prospective randomized trials have evaluated adjuvant RT in patients with endometrial cancer after surgery. These are summarized in Table 1. Patients included in these studies had low- to intermediate-risk disease. The earliest of the three trials was a Norwegian study by Aalders et al. and included 540 patients with stages IA and IB tumors (FIGO 2009 staging) of all grades (Aalders et al. 1980). In this trial, patients were randomized to receive pelvic radiation to a dose of 4000 cGy or observation. Both arms of the study received vaginal brachytherapy to a dose of 6000 cGy to the vaginal surface. The PORTEC-1 study included 714 patients with stage IA grade 2–3 and also IB grade 1–2 tumors (Creutzberg et al. 2000). Patients were randomized to observation versus pelvic RT to a dose of 4500 cGy in 25 fractions. The GOG 99 trial (Keys et al. 2004) included 392 patients with stages IA, IB, and II

Table 1 Prospective randomized trials evaluating adjuvant RT in patients with endometrial cancer after surgery

Study	No patients	Treatment arms	Local recurrence	Survival
Aalders et al. (1980)	540	Brachy (60 Gy) vs brachy + RT (40 Gy)	6.9 % vs 1.9 % $P < 0.05$	89 % vs 91 % $p > 0.05$
PORTEC-1 (Creutzberg et al. 2000)	714	Observation vs RT	14 % vs 5 % $P < 0.05$	85 % vs 81 % $p > 0.05$
GOG 99 (Keys et al. 2004)	392	Observation vs RT	12 % vs 3 % $P < 0.05$	86 % vs 92 % $p > 0.05$
ASTEC/EN5 (Group et al. 2009)	915	Observation vs RT (53 % of patients received brachytherapy)	6.1 % vs 3.2 % $P < 0.05$	84 % vs 84 % $p > 0.05$

tumors of all grades. Patients received pelvic and para-aortic lymph node sampling and were randomized to observation or pelvic RT to a dose of 5040 cGy in 28 fractions. The ASTEC/EN5 study included 915 patients with IA grade 3 tumors and IB and II tumors of all grades (Group et al. 2009). Papillary serous carcinomas were also included in this study. Patients were randomized between adjuvant RT and observation. Brachytherapy was allowed in both arms as per center policy. All four trials showed a benefit in local control; however, no survival improvement was seen. However, there is a subset of patients who are at a high risk of recurrence that potentially would have a survival improvement with adjuvant RT. Most patients in these trials had low-grade and early stage disease with a low risk of recurrence. This may have contributed to the dilution of a potential effect on survival in these studies.

2.1.2 High-Intermediate-Risk Group

In PORTEC-1, central pathology review found that 60 % of patients in the study had grade 1 disease with only 8 % with grade 3. Also, those with both grade 3 tumors and outer-half myometrial invasion were not included in the study. Therefore, most patients were at a low risk of recurrence. The study did identify a group of patients considered to be at high-intermediate risk, defined as having 2 or more risk factors which included age > 60, more than 50 % myometrial invasion, and grade 3 tumors. The relapse rate of this group was 20 % with no RT and 5 % with pelvic RT (Creutzberg et al. 2011). In the GOG 99 study, similarly a high-risk group was identified. These included patients with 3 risk factors, patients over age 50 with 2 risk factors, and patients over age 60 with 1 risk factor. The risk factors in the study were age over 70, grade 2 or 3 tumors, over 66 % myometrial invasion, and lymphovascular space invasion. For this group, no adjuvant RT yielded a rate of relapse of 27 % and the RT arm relapse was 13 %. Therefore, the high-risk groups as defined in the PORTEC-1 and GOG 99 studies do relapse at a higher rate, and RT seems to significantly lower this risk of relapse. Although not proven, these patients may be a subset that may have a survival advantage with adjuvant RT treatment after surgery. In the GOG 99 study, there was in fact a trend towards a survival benefit for the high-risk group; however, it is also important to note that neither study was powered to show a survival benefit.

2.1.3 Vaginal Vault Brachytherapy

Many patients with intermediate-risk disease are considered for vaginal brachytherapy. The PORTEC-2 study randomized 427 patients to vaginal brachytherapy and external beam radiation. Patients that were included in this study had IA grade 3 tumors and also IB grade 1 and grade 2 tumors (Nout et al. 2010). Results showed that vaginal relapse rates were low in both the brachytherapy and pelvic RT patients (1.8 %, 1.6 %, $p = 0.7$) with no differences in overall or relapse-free survival. However, there was found to be a higher pelvic relapse rate in the vaginal brachytherapy arm as compared to the pelvic RT arm (3.8 %, 0.5 %, $p = 0.02$ %). Therefore, a small subset of patients will recur in pelvis if left untreated, and the challenge is identifying this group as nodal recurrences would make salvage treatment challenging. Also, only 12 % of patients in the PORTEC-2 study had disease with lymphovascular space invasion (LVSI). LVSI has been found to be a strong predictor of pelvic and distant disease particularly when quantified as "substantial LVSI" as recently presented by the authors of the original PORTEC studies (Nout et al. 2014). However, from the overall results of PORTEC-2, there exists a practice of vaginal vault brachytherapy treatment for most patients with intermediate-risk and high-intermediate-risk disease despite the presence of other risk factors such as LVSI status, as patients with vault treatment have been found to have an improvement in quality of life with decreased bowel symptoms and better social functioning (Nout et al. 2009). For high-risk patients, there is an interest in combining vault brachytherapy with chemotherapy with the goal of avoiding pelvic RT treatment for these patients as well. Results from the GOG 0249 trial were recently presented (McMeekin et al. 2014). This study randomized patients with high-risk endometrial cancer as per the GOG 99 criteria to vaginal vault brachytherapy

with paclitaxel and carboplatin chemotherapy versus pelvic RT. The results presented showed no difference in outcome for the two treatments with worst acute toxicity in the vault brachytherapy and chemotherapy arm.

2.1.4 Salvage Radiation Therapy

The current PORTEC-4 study evaluates two vaginal brachytherapy dose schedules and observation in high-intermediate-risk patients. The rationale of the observation arm in this study is the lack of survival benefit found in the randomized trials and the thought that most isolated vaginal recurrences can be salvaged successfully. In PORTEC-1, it was found that 75 % of locoregional relapses could be treated for curative intent and 85 % reached a complete remission. The 3-year survival was found to be 73 % after isolated vaginal relapse (Creutzberg et al. 2003). The GOG 99 study, on the other hand, had 13 patients with isolated vaginal recurrences and 12 were treated with salvage radiation. Crude observations showed that 5 of those patients had died from endometrial cancer. Other studies have also found lower survival rates for isolated vaginal recurrences as compared to the PORTEC data (Jhingran et al. 2003; Wylie et al. 2000). For example, Jhingran et al. found in a cohort of 91 patients that the 5-year survival for patients with isolated vaginal recurrences was 43 % (Jhingran et al. 2003). Furthermore, 9 % of patients had grade 4 complications of RT requiring surgery. Other studies have supported the risk of toxicity in salvage treatment, with grade 3 and 4 toxicities found to be as high as 18 % (Petignat et al. 2006). Therefore, the salvage rate of vaginal recurrences may not be as high as previously found, while the significant risk of grade 3 and 4 toxicities exists in this treatment. Patients should be carefully selected when considering observation over adjuvant RT, and future results from the PORTEC-4 trial may help in guiding management in these cases.

2.2 Advanced Uterine Cancer

For patients with advanced stage III or IV endometrial cancer, variation in practices has ranged from systemic chemotherapy treatment alone, radiation alone, to a combined modality approach. There is very little consensus on the management of this diverse population of patients, and current ongoing clinical trials are evaluating the role of both treatment modalities. In the past, patients with advanced stage disease were typically treated with pelvic or abdominal RT after surgery. The GOG 122 study randomized patients to whole abdominal radiation or a combination of doxorubicin and cisplatin (Randall et al. 2006). Chemotherapy was found to significantly improve progression-free and overall survival as compared with whole abdominal RT. However, recurrence rates were found to be high, at 50 % and 54 % in the chemotherapy and RT arm, respectively. Furthermore, patients treated with chemotherapy alone relapsed at a rate of 18 % in the pelvis. Although this study contributed to the shift towards chemotherapy as the standard of care in many practices, the RT dose may not have been adequate for all patients. Residual disease was allowed in this study, and the total dose of RT given was 30 Gy to the abdomen with a boost to the tumor of 15 Gy. The maximum dose to any residual disease would therefore be 45 Gy which is typically considered a dose for microscopic disease rather than gross tumor. The dose chosen in GOG 122 is very reasonable given that the RT arm was given whole abdominal radiotherapy. However, the more standard approach would be pelvic RT with possible para-aortic radiation, a strategy that would lead to an improved tolerance of RT with higher doses (only 84 % of patients completed the whole abdominal RT). Therefore, the role of adjuvant pelvic RT for patients with no residual disease after surgery is still in question. An Italian study by Maggi et al. randomized 340 patients with high-risk and advanced disease to chemotherapy (cisplatin, doxorubicin, and cyclophosphamide) and pelvic RT. The study found that combination chemotherapy was not superior to pelvic RT in terms of survival (Maggi et al. 2006). Radiation delayed local relapse and chemotherapy delayed distant relapses, but these were not found to be significant. As local recurrences are often the issue in treatment with chemotherapy alone and distant recurrences in radiation alone, it would be of interest to combine

chemotherapy with radiation to address both microscopic pelvic and distant disease.

The current GOG 258 study is evaluating the role of chemoradiation and adjuvant chemotherapy in advanced optimally debulked endometrial cancer. In this study, patients are randomized between volume-directed radiation with concurrent cisplatin followed by carboplatin and paclitaxel versus carboplatin and paclitaxel for 6 cycles. The PORTEC-3 study compares concurrent chemoradiation with cisplatin and adjuvant carboplatin and paclitaxel with pelvic RT alone in high-risk and advanced stage uterine carcinoma patients. Although there still exists much debate regarding adjuvant treatment of uterine carcinoma patients, current prospective studies may provide insight into the optimal management for these patients which likely will involve a combined modality approach.

3 Uterine Sarcomas

Uterine sarcomas are rare malignancies consisting of only 5 % of all uterine cancers and include different histological subtypes of carcinosarcomas, leiomyosarcomas, and endometrial stromal sarcomas. Because of this heterogeneous group of patients and its rarity, there is a paucity of evidence to guide adjuvant radiation treatment. Two randomized trials have evaluated the role of RT after surgery for these patients (Reed et al. 2008; Wolfson et al. 2007). The EORTC study randomized 224 patients to observation or pelvic RT. It was found that radiation did not influence survival but did improve local control in the carcinosarcoma patients. Leiomyosarcoma patients did not have a benefit with radiation in either survival or local control (Reed et al. 2008) (there was too few number of endometrial stromal sarcoma patients to properly analyze). GOG 150 compared whole abdominal radiation to cisplatin, ifosfamide, and mesna (CIM) chemotherapy in advanced carcinosarcoma patients (Wolfson et al. 2007). No statistically significant difference in survival or local recurrence was found in either group. It should be noted, however, that the radiation treatment in this study consisted of 30.6 Gy to the abdomen which was likely insufficient to control microscopic disease. As a result, there was a high rate of abdominal recurrences in the radiotherapy arm.

From these randomized studies, there is no consensus on optimal management of endometrial sarcomas. Based on the EORTC study and retrospective evidence, most radiation oncologists would offer pelvic RT to carcinosarcoma patients to decrease the risk of local recurrence. A database analysis by Sampath et al. of 3650 patients with uterine sarcoma has shown a 60 % risk reduction with RT (Sampath et al. 2010). There was a significant benefit in local recurrence with carcinosarcoma patients in this study as well. For leiomyosarcoma patients, the EORTC study did not show a local control benefit from radiation, but again the study by Sampath et al. found a reduction in local recurrence rate from 16 to 2 % after RT. A recent retrospective study of 69 patients in a single institution found that postoperative RT reduced local recurrence rates from 39 to 19 % at 3 years and improved overall survival on univariate analysis (Wong et al. 2013).

Given the rarity of this disease, there is still much controversy regarding adjuvant RT for uterine sarcomas. No survival benefit has been found in both prospective and retrospective studies; however, carcinosarcomas seem to benefit in local control with radiation. There seems to also be an effect in the local control of leiomyosarcomas; however, this is only found in retrospective trials.

4 Cervical Cancer

There will be an estimated 12,360 new cases of cervical cancer diagnosed in the USA in 2015, with one third of that number dying from cancer according to the NCI-SEER statistics (Siegel et al. 2014). While the incidence of cervical cancer in the USA has been gradually declining as a result of widespread screening, outcomes still remain poor for many with cervical cancer. In addition, there has been a negligible survival improvement over the past decade (Howlader et al. 2013). Internationally, cervical cancer is the

fourth most common cancer in women (with 528,000 new cases reported per year) and extremely lethal (with a mortality incidence ratio of 52 %) (WHO 2014; GLOBOCAN 2012). Cervical cancer is staged clinically using the FIGO system developed by the International Federation of Gynecology and Obstetrics (FIGO) (Pecorelli et al. 2009). The management of cervical cancer depends upon the FIGO stage at presentation. Early stage (including IB1) tumors are treated by radical surgical resection with nodal staging. Adjuvant radiation and +/− chemotherapy are also indicated based upon poor prognostic pathologic factors like depth of stromal invasion, LVI, positive margins, and positive nodes (Oncology NCCNCPGi 2014).

4.1 Locally Advanced Cervical Cancer (LACC) (FIGO Stage IB2-IVA)

Cervical cancer that is not primarily surgically resectable at presentation is termed as LACC and is the most common presentation in developing countries the world over. It is still not an uncommon diagnosis in the USA with over 50 % of patients still present at an advanced stage, often with nodal metastases (Howlader et al. 2014). Radiation therapy in conjunction with radiosensitizing chemotherapy is the primary modality for treatment of this type of cervical cancer (Oncology NCCNCPGi 2014).

Several prospective randomized trials compared concurrent chemotherapy and radiation to radiation alone for advanced cervical cancer and showed substantial improvement in local control and overall survival in the late 90s (Wang et al. 2011; Eifel et al. 2004). As a result, the National Cancer Institute issued a treatment alert in 1999 establishing chemoradiation as the standard of care for advanced cervical cancer (Thomas 1999). Radiotherapy for cervical cancer currently consists of radiation in the form of external beam delivered over 5–6 weeks of daily therapy followed by or interdigitated with intracavitary or, less frequently, interstitial brachytherapy. Brachytherapy is an integral part of the radiation treatment for cervical cancer. It is a historical treatment for cervical cancer and has been shown in several series to be absolutely essential for local control and survival (Tanderup et al. 2014a; Montana et al. 1995; Han et al. 2013).

4.1.1 Brachytherapy for Cervical Cancer

Image-Based Three-Dimensional Brachytherapy: MRI or CT? The most updated American Brachytherapy Society (ABS) guidelines (Viswanathan et al. 2012) clearly outline the evolution of intracavitary brachytherapy from low-dose rate to mostly HDR (high-dose rate) and pulsed-dose-rate (PDR) brachytherapy. By the use of computerized planning, multiple dwell positions, and times, these allow more precise shaping of the dose distribution to the extent desired by the radiation oncologist. The ABS document states that the most commonly used regimens in the USA are 45 Gy external beam pelvic radiation pelvis (possibly with a sidewall boost) with concurrent cisplatin-based chemotherapy and followed by an HDR brachytherapy boost of five fractions – either 5.5 Gy per fraction (for patients having <4 cm of residual disease) or 6 Gy (for patients with tumors >4 cm after EBRT) (Viswanathan et al. 2012).

These prescriptions refer to point A modification of the classical Manchester 2-dimensional system point A (Nag et al. 2000) for tumor coverage and have been shown to underestimate dose to large tumors as well as have poor correlation to critical organ toxicity (Katz and Eifel 2000). Computed tomography (CT)-based three-dimensional (3D) external beam planning has been utilized since 2000, and this initially led to slow incorporation of CT scan use in intracavitary brachytherapy (as a replacement for plane X-rays) while still being anchored in the 2-dimensional Manchester system.

Studies have compared X-ray-based 2D and CT-based 3-dimensional HDR and showed better cervical tumor coverage (with smaller tumors) and dosimetrically superior critical organ point doses with 3D imaging (Kim and Pareek 2003;

Table 2 Dose limits to CTV and OAR

Dose specified to	3D imaging (CT/MR)
Point A	Variable (depends upon tumor size)
D90 of CTV-cervix (HR-CTV)	>80 and <90 Gy EQD2
D2cc bladder	<90 Gy EQD2 (lower better)
D2cc rectum	<75 Gy EQD2
D2cc sigmoid	<75 Gy EQD2

(Modified from ABS/GEC-ESTRO guidelines, Viswanathan et al. 2012; Kirisits et al. 2005)
EQD2 2Gy/fraction normalized therapy dose; 3D three dimensional

Gao et al. 2010). Initially, the use of imaging for tumor delineation was proposed with a DVH system similar to external beam targets (Nag et al. 2004). This new paradigm was extensively developed, championed, and implemented by the group from Vienna (Potter et al. 2006) under the aegis of Groupe European de Curietherapie-European Society for Therapeutic Radiology and Oncology Working Group (GEC- ESTRO). These were all MR-based plans highlighting the cervical tumor on T2W images (with superior soft tissue contrast and tumor enhancement) and bringing brachytherapy to a modern volumetric era (Haie-Meder et al. 2009; Lindegaard et al. 2008; Kirisits et al. 2005). The Vienna group have shown the benefits in this series compared to historical series improving LC and PFS (Lindegaard et al. 2008; Potter et al. 2007). The GEC-ESTRO have also defined clinical tumor volumes (HR-CTV) and established dose volumes for organs at risk (OAR) of toxicity (Potter et al. 2006; Kirisits et al. 2005) which have been adopted by ABS (see Table 2).

Table 2 shows the new definitions and recommended summated dose to the OAR which would permit low toxicity.

The updated results from the Vienna group which advocates MR-based planning for each fraction (7 Gy×4) using high-risk CTV concept (D90) with a goal of D90 of >85 GY to the HR-CTV (Potter et al. 2011). In their series of 156 consecutive patients with advanced cervical cancer, local control was 95 % at 3 years and also excellent at 86 % for FIGO IIIB. However, complex hybrid interstitial techniques with online MRI were required in 45 %, thus increasing the complexity of necessary hardware and infrastructure for standard intracavitary brachytherapy. Though the authors conclude that there was some impact on survival – probably for smaller tumors and earlier stages – the overall survival was still a modest 45 % for IIIB group of patients at 3 years. MRI-based brachytherapy is an expensive resource-intensive form of therapy even in the USA. It does prolong the treatment time and discomfort to the patient and may not be completely applicable for large volumes of patients with cervical cancer, particularly in patients from less developed countries. The results of the GEC-ESTRO group have created a sense of urgency among brachytherapists to begin utilizing MR planning in their practice; however, logistics and practicalities of this implementation are considerable, not to mention the increasing cost to health care.

Hence, CT-based approaches have been looked at and have many important benefits, the most important of all being that the CT scanner is readily available in radiation oncology departments. CT-based 3D HDR brachytherapy is particularly optimal for smaller cervical cancers, where often point A is far lateral to tumor edge. This makes it possible to achieve high target coverage and lower OAR dose since the OARs are seen clearly on CT and one can contour them and maintain D2 cc doses (Vargo and Beriwal 2014).

The prospective French STIC (Soutien aux Techniques Innovantes et Coûteuses) study with over 600 advanced cervical cancer patients utilized mostly CT scan for planning 3-D PDR brachytherapy based on GEC-ESTRO volumetric guidelines and compared this with 2-D planned patients (Charra-Brunaud et al. 2012). At a median 2-year follow-up, 3D planning significantly improved local (78.5–100 % vs 73.9–91.9 %, $P=0.003$) and locoregional (69.6–96.1 % vs 61.2–87.9 %, $P=0.001$) relapse-free survival, with trends towards improved disease-free and overall survival. 3D brachytherapy also statistically significantly decreased grade 3+ urinary (1.2–5.5 % vs 5.8–9.2 %, $P=0.02$), gynecologic (1.4–7.5 % vs 5.7–15.4 %, $P=0.01$) toxicities. As

CT scan is unable to clearly delineate the cervix or tumor (compared to the enhancement seen on T2W-MRI), attempts have been made to reach a consensus on CT contouring.

To address these concerns, a group of experts compared CT to MRI-based planning showing that tumor height, thickness, and total volume measurements as determined by CT were not significantly different compared with the MRI volumes. However, the width measurements differed in HR-CTV for CT (larger) vs MRI (smaller) planning, resulting in statistically significant differences in the volume treated to the prescription dose or greater (MRI 96 % vs CT 86 %, $P = 0.01$) and dose to 90 % of the treatment volume (MRI 8.7 % vs CT 6.7 %, $P < 0.01$) (Viswanathan et al. 2007). A recent cooperative group attempt at consensus HR-CTV contouring of CT and MR imaging for cervical tumors also showed larger volumes for CT but no statistically significant difference in dose coverage to tumor and OAR's. This study had predominantly smaller tumors (Viswanathan et al. 2014). For the majority of the patients with smaller tumors, CT-based planning is sufficient and is recommended because of the multiple advantages of avoiding perforation, a lower *OAR* doses, and possibly better coverage of the target.

Combined MR-CT Approach A more practical approach to incorporate benefits of MR imaging was explored by the University of Pittsburgh (Beriwal et al. 2011) with the first implant performed by MRI planning and subsequent one by CT-MR fusion planning; early results have shown the feasibility of this approach with excellent local control. The Vienna group also used the same hybrid technique incorporating automated applicator-based image registration (Nesvacil et al. 2013); there was small systemic underestimation with the hybrid approach (MR-CT fusion) compared to the MR "gold standard." All the outliers where the difference in D90 was greater than 1 Gy had large tumors requiring more complex applications (including Vienna applicator – which is a combined tandem and ring with interstitial needles) (Kirisits et al. 2006); thus, the MR-CT approach is best for small tumors and may not be adequate for complex tumors. It must be noted that performing an MRI (with applicator in place) without the capability to target complex parametrial tumor extension using the Vienna hybrid interstitial applicator or other form of interstitial platform will negate the benefits of better visualization by MRI.

Most recently, the GEC-ESTRO conducted an international clinical trial called the Embrace Trial which is a prospective study of the role of MR brachytherapy in cervical carcinoma in a multi-institutional, multi-international setting. Recently, two reports of this trial were presented highlighting the importance of MR brachytherapy and where it would be most beneficial. The first analysis looking at stage IIB patients showed that for small- to intermediate-size tumors that are gross at diagnosis on initial MRI (GTVd <40 cc) and with mean clinical target at the time of brachytherapy (HR-CTV <30 cc), there was no residual parametrial disease at brachytherapy. These two groups have essentially small central tumors which could possibly be treated well with CT-based brachytherapy, and MRI may not be required in these situations. An initial MR at diagnosis would probably identify this group of patients and circumvent the need for MR brachytherapy in areas of low resource availability (Jastaniyah et al. 2014). The second report correlated HR-CTV D90 dose with HR-CTV volume of 30 cc suggesting that to achieve 90 % control rate for larger (>30 cc) tumors, D90 should be ≥90 Gy, indicating that these larger residual tumors require more complex MR-guided intracavitary-interstitial approach which splays out the dose in the parametrium, the absence of which is the primary cause of failure in standard intracavitary pear-shaped distributions (Tanderup et al. 2014b).

4.1.2 Para-aortic Nodal Metastases from Cervical Cancer: Prophylaxis and Control

Para-aortic lymph node metastasis (PALN) in locally advanced cervical carcinoma is a strong indicator of poor prognosis and reduced survival (Hoffman et al. 2012; Expert Panel on Radiation

O-G et al. 2013). Traditionally, patients with PALN have been excluded from most clinical studies looking at the role of combined modalities of chemotherapy and radiation therapy. For instance, patients with positive PALN on pretreatment staging or by imaging were excluded from all the landmark chemoradiation studies published in 2000 (Eifel et al. 2004; Rose et al. 2007). However, there is a subgroup of patients who have disease limited to PALN, and these can potentially have a longer progression-free survival (PFS) with comprehensive extended-field radiation therapy (EFRT) (Small et al. 2007; Kim et al. 2009). Currently, PALN are assessed by imaging methods, preferably PET scan (Rose et al. 1999).

Following the NCI consensus chemoradiation statement (Thomas 1999), there is an uncertainty about how to treat patients with pelvic lymph nodes positive on pretreatment imaging. Generally, because of the absence of a prophylactic extended field in the RTOG and GOG chemoradiation studies, there is no uniform recommendation about prophylactic radiation of PALN nodes for patients with positive pelvic or iliac nodes (who are at high risk of having occult PALN metastasis). In the RTOG 90–01 trial (Eifel et al. 2004) comparing pelvic chemoradiation to pelvic and prophylactic extended field radiation, the reported risk of PALN failure was 7 % vs 4 % at 5 years but projected to be 9 % vs 4 % at 8 years (double the risk for the group not receiving EFRT). In addition, although the 2 arms were randomized, two thirds of the patients on the study had negative pelvic nodes on pretreatment staging. The risk of PALN failure would probably have been higher in a cohort of patients with positive pelvic nodes undergoing pelvic chemoradiation alone, begging the question whether there is a role for prophylactic EFRT combined with radiosensitizing chemotherapy in this class of patients.

While PET and PET-CT is the current imaging standard of care for staging PALN metastases from cervical cancer, it still has many limitations. Based on a recent meta-analysis (Choi et al. 2010), the maximum sensitivity was 82 %, with a false-negative rate of 12–15 % because of limited resolution in the detection of subcentimeter nodes (Gouy et al. 2013). Given that PET may not always pick up these smaller PALN metastases, it may be reasonable to include PALN EFRT in patients most at risk – with high iliac or pelvic nodes with large tumors (Kang et al. 2013; Inoue and Morita 1995). A recent randomized trial compared extended-field concurrent chemoradiation (EF-CCRT) to standard whole-pelvis concurrent chemoradiation (WP-CCRT) in locally advanced cervical cancer (stage IIB-IVA), with radiologic negative para-aortic lymph nodes (PALNs) (Asiri et al. 2014). With a median 60-month follow-up. overall PALN, distant-metastasis control, disease-free survival, and overall survival rates were 97.1 %, 86.9 %, 80.3 %, and 72.4 % in EF-CCRT, respectively, in comparison with WP-CCRT (82.1 %,74.7 %, 69.1 %, and 60.4 %), with P-values of 0.02, 0.03, 0.03, and 0.04, respectively. No difference in acute toxicity profile was seen between the groups, and late toxicities were mild and minimal.

The second controversy arises about the extent of treatment of the PALN region in patients who have limited lower PALN metastases. Again there is no clear consensus about what is the best thing to do. In the most recent cooperative group international outback study (ANZGOG0902 2015), for example, which is looking at the addition of adjuvant chemotherapy in patients with locally advanced cervical carcinoma, patients with lymph nodes above L3–L4 are excluded. This classification potentially includes patients who have lower para-aortic nodal metastasis. The protocol recommends extending radiation field in these cases to encompass the highest involved node with a margin of 3 cm or one vertebral body cephalad to a maximum upper level of L1/L2 vertebral space. No mention is made of treating the entire PALN chain. In practice, there is wide variation in the amount of PALN chain treated in patients with low PALN lymph nodes. This is probably because of higher perceived toxicity with EF-CRT. In the absence of proper consensus and peer recommendation, it is probably prudent to include the entire para-aortic chain up to T11–12 interspace (Small et al. 2007). The NCCN guidelines do recommend PALN chain radiation

in the presence of PALN metastasis, but there is no mention of a prophylactic EFRT (Oncology NCCNCPGi 2014).

Extended-Field Radiation Therapy (EFRT) In the modern setting of intensity-modulated radiation therapy, one can safely target this area and minimize the toxicity for these patients. The use of modern 3-dimensional techniques (Kim et al. 2009) and more recently IMRT has enabled better PALN coverage while reducing toxicity and improved survival compared to traditional 2-dimensional EFRT (Du et al. 2010; Rash et al. 2013; Zhang et al. 2014). The series by Du et al., for instance, 58.8 % vs 25 % 2-year survival for IMRT with a reduction in acute and late grades 3–4 GI toxicity (3.6 % vs 19 % acute GI toxicity, 0 % vs 19 % late GI toxicity) (Du et al. 2010).

Controversies exist regarding the radiation dose required to control PALN metastases. The American College of Radiology expert panel recommends boosting all nodal disease to a range between 56 and 65 Gy (Gaffney et al. 2011), but according to series by Rash et al., a minimum dose of 54 Gy appears to be effective in controlling macroscopic nodal disease (Rash et al. 2013). A dose of >60 Gy would be recommended for nodes >2 cm in size if safe delivery were possible using complex radiation delivery techniques and, if possible, the bowel point dose to less than 55 Gy. The technique of simultaneous integrated nodal boost may allow for a higher conformality to the lymph nodes; however, with this technique, regression of the lymph nodes does occur, and this may result in a higher than planned bowel dose (Cihoric et al. 2014).

Finally, there is a perception among gynecologic oncologists that lymph nodes greater than 2 cm cannot be safely and adequately targeted with radiation alone. This was certainly true using traditional 2-dimensional radiation techniques in older series (Stryker and Mortel 2000). The development of robotic equipment and minimally invasive surgical techniques surgery over the past decade has resurrected interest in PALN staging and debulking (Bats et al. 2014; Gocmen et al. 2014). To date, the survival advantage following surgical resection of grossly enlarged PALN appears to be limited (Kim et al. 2009; Cosin et al. 1998; Goff et al. 1999; Hacker et al. 1995). Based upon previous nodal demographic studies, Kupets et al. concluded that only 2 % of patients with stage IIB and 4 % patients with stage IIIB would benefit from pelvic node debulking, assuming a 100 % resectability rate at surgery (Kupets et al. 2002). In reality, a large percentage of bulky nodal disease is unresectable negating the benefit of surgery.

4.1.3 Pelvic Intensity-Modulated Radiation Therapy (IMRT) for Intact Cervical Cancer

Traditional radiation for pelvic-confined cervical cancer includes large pelvic radiation ports to encompass the pelvic lymphatics and the potential for cervical tumor target motion. IMRT for cervical cancer involves inverse planned beam intensity modulation producing complex radiation dose distributions to achieve optimal target coverage. Like IMRT for other sites, after contouring target volumes and critical structures, dosimetric and volumetric requirements are defined. The planning computer then follows a process of stepwise calculations to achieve the goal requested. The resultant dose cloud which conforms to the concave or convex shape of the target producing steep dose gradients away from normal tissues provides conformality and normal organ sparing. While this potentially reduces the dose to normal organs at risk (OAR), there are some problems with the intact cervical tumors which make this controversial (Wagner et al. 2013; Chan et al. 2008). Due to the dynamic nature of tumor response in cervical cancer and the mobility of the adjacent OAR and uterus, the IMRT target potentially changes during the course of treatment (Beadle et al. 2009). As the tumor responds, areas that were in the target PTV now get encroached upon by bowel, and this could result in an increased dose of these normal structures (van de Bunt et al. 2008). In addition, interfraction motion of target CTV (uterus and cervix) will impact on dose coverage with tight margins of IMRT. Fortunately, intra-fraction motion is minimal (based on sequential cine-MR image

studies from Princess Margaret Hospital) allowing for PTV margins of 0.5 (Chan et al. 2008). However, inter-fraction motion and organ changes will require daily imaging with a plan for adaptation thru the course of treatment if tight margins are utilized. Another more common approach in the published series is to use wide PTV margins (1–2 cm) for the cervix CTV to account for tumor regression and organ motion, while using more limited margins for the pelvic nodal PTV in the form of a *wide-field hybrid* IMRT covering the changing cervix CTV with the lesser goal of bowel and possibly bone marrow sparing to reduce the acute/chronic toxicities of pelvic RT (Mundt et al. 2002). We will focus only on clinical studies and not dosimetric reports. While the latter have shown a benefit for IMRT, they do not account for organ motion effects.

For intact cervical cancer, there is very limited data available on outcomes, which is mostly retrospective (Chen et al. 2011; Beriwal et al. 2007). These studies generally had wide CTV and PTV margins (average 1–1.5 cm) without daily IGRT or replanning. One of the largest series prospectively published is by Kidd (Kidd et al. 2010). This prospective cohort study included 452 patients with newly diagnosed cervical cancer treated with curative intent external irradiation (+ concurrent chemotherapy) and brachytherapy (135 IMRT and 317 non-IMRT). All IMRT patients underwent an F-18 fluorodeoxyglucose positron emission tomography (FDG-PET/CT) simulation. On analysis, the IMRT and non-IMRT groups had similar stage distribution and histology. For all patients, posttreatment FDG-PET findings were not significantly different between the IMRT and non-IMRT patients ($p=0.9774$). The mean follow-up for all patients alive at the time of the last follow-up was 52 months (72 months non-IMRT, 22 months IMRT). The difference in recurrence-free survival between the two groups did not reach statistical significance ($p=0.0738$), although the IMRT group showed better actuarial overall and cause-specific survivals ($p<0.0001$). The absence of long-term follow-up for the IMRT group makes the conclusion of better overall survival somewhat premature though. The risk of severe (grade 3–4) toxicity was significantly less for patients treated with IMRT. There was no significant recurrence-free survival difference for the 2 groups. This series had a different treatment schema with the cervix CTV (defined as a PET metabolic tumor volume) receiving only 20 GY with additional tumoricidal dose delivered by brachytherapy per the institutional policy. No mention is made about margins and image guidance for the cervix CTV (MTV) which has been shown to be an issue in other series.

Another prospective series is the second national Nordic protocol (better called a registry) for locally advanced cervical cancer (Lindegaard et al. 2013). In 2005 image-guided adaptive brachytherapy (IGABT) based on magnetic resonance imaging (MRI) and optimization of the BT dose distribution to the remaining tumor and cervix at time of BT (HR-CTV) was introduced in Aarhus (second national protocol). In 2008, SIB-IMRT (simultaneous integrated boost) was introduced as a routine technique (50 gy/30 fx to elective nodal and tumor areas and 60 gy to nodal boosts). Large margins of 1 cm+were used to create a homogenous central pelvic dose (similar to other wide-field IMRT series). The second cohort had reduced toxicity Gr2 gastrointestinal toxicity compared to the prior protocol which could be attributed to IMRT. Pelvic control was maintained in 2 cohorts – so IMRT was not detrimental (Lindegaard et al. 2013).

Prospective clinical trials are limited – one small randomized published trial from India with <50 patients with locally advanced intact cervical cancer receiving 50.4 Gy in 28 fractions IMRT vs pelvic conventional 4-field RT showed less chronic gastrointestinal toxicity (13.6% vs 50%, $P=.011$) – with no significant difference in disease control or survival (Gandhi et al. 2013). What has been reassuring is that all the reported pelvic IMRT clinical series mentioned report locoregional failure rates of 15–20% at 2–3 years which is similar to those from randomized trials (Eifel et al. 2004; Rose and Eifel 2001). In addition, although the reported clinical IMRT series have used wide margins to compensate for tumor motion and regression, IMRT has been shown reduced bowel toxicity (Chen et al. 2011; Hasselle et al. 2011) and hematologic toxicity as well (Lujan et al. 2003) which adds to the utility of this treatment delivery technique. An

important role for IMRT integration is boosting nodal disease (discussed in section on para-aortic nodes).

While IMRT for intact cervix is being utilized more commonly in practice, very few guidelines exist regarding contouring, image guidance, and adaptive planning for this site. Lim et al. (2011) described MRI-based consensus cervix CTV contouring for IMRT planning. Besides including the uterus, adnexa, parametrium, and cervix, the recommendation was to include the mesorectum as well if the uterosacral ligament was involved (effectively leading to the entire rectum being in the PTV). For the nodal CTV, contours and margins were according to the RTOG atlas.

PTV margins of 1.5–2 cm around the CTV were recommended with daily soft tissue verification which was available during treatment. The consensus was that the use of IMRT without any form of daily soft tissue verification risked geographical target miss and should be approached with caution. This report did not address tumor regression and inter-fractional motion for which or adaptive replanning will be important if the benefits of narrow-margin intensity-modulated radiotherapy are to be maximized in women with cervical cancer (Wagner et al. 2013).

Strategies to account for these uncertainties include creating a library of plans (based upon organ and tumor motion) which could be utilized based upon a daily cone-beam CT evaluation of cervix CTV (Heijkoop et al. 2014).

Another more resource-intensive approach involves weekly MRI and novel, dosimetry-triggered adaptive IMRT strategy which requires dose deformation (Lim et al. 2014).

5 Vulvar Cancer

Surgery has been established as a primary treatment modality in vulva cancer. The role of radiation consists of adjuvant, neoadjuvant, or definitive treatment for the primary lesion and lymph nodes. Although its role has been increasing over the last 30 years, there is still a wide variation in radiation oncology practice for this gynecologic malignancy. Adjuvant RT to the primary is controversial since the ability to successfully salvage a local recurrence of vulva with surgery is high. Definitive RT can be indicated for locally advanced, unresectable vulvar cancers; however, the treatment of groins in this setting is also of debate. IMRT techniques for vulva radiation are emerging however discussion in regard to treatment volume and efficacy.

5.1 Early Stage Vulvar Cancer

5.1.1 Adjuvant Groin RT

Adjuvant RT to the groins and pelvis has been shown to improve outcomes in patients with positive lymph nodes after groin dissection. GOG 37 randomized 114 patients with squamous cell carcinoma of the vulva to groin and pelvic RT versus ipsilateral lymph node dissection with surgery (Kunos et al. 2009; Homesley et al. 1986). RT consisted of 45–50 Gy to the pelvis. This study found both a survival and local control benefit in patients treated with radiation. Groin relapse in the surgery arm was 24% as compared to 5% in the RT arm. This likely translated into the survival benefit (36% vs 6% 6 years) seen in this study as groin recurrences mostly resulted in death. The benefit for RT has been seen in the first publication for 2 or more lymph nodes and in the updated publication for over 20% positive lymph nodes (Kunos et al. 2009). The study was, however, not powered to detect a benefit in 1 lymph node or more.

A retrospective SEER database study has shown that there is a survival benefit in 1 lymph node or more (Parthasarathy et al. 2006). Other observational studies have found that extranodal extension and nodal disease >=5 mm may indicate worse outcomes in patients with a single positive node, and this may help guide recommendations in regard to adjuvant RT for patients with a single positive node (Origoni et al. 1992; Paladini et al. 1994; van der Velden et al. 1995).

5.1.2 Adjuvant Primary RT

Surgery is considered to be the principal management for addressing the vulvar primary tumor. Pathological factors that predict for recurrence have been found in observational studies. Heaps

et al. showed that close margin status was most powerful in predicting vulvar recurrence as the recurrence rate is approximately 50% with a pathological margin of <8 mm. Other factors included lymphovascular space invasion (LVSI), depth of invasion, tumor thickness, infiltrative growth, keratin, and mitosis (Heaps et al. 1990).

Even with the presence of close margins or positive margins and the above risk factors, there is debate in regard to the benefit of adjuvant RT. With close follow-up and monitoring, vulvar recurrences can be successfully salvaged with surgery. Therefore, one would argue that the patient would be spared the toxicities of radiotherapy unless the recurrence is deemed unresectable. The issue with this approach is that patient compliance to a close follow-up schedule is required, and deep recurrences may be difficult to detect clinically. Furthermore, when there are multiple risk factors for recurrence, it may be that additional surgery will not be sufficient to prevent another recurrence and adjuvant RT to the tumor bed may offer a benefit. Also, poor survival rates are seen in patients who recur locally after surgery (Heaps et al. 1990).

A retrospective study of 62 patients with close or positive margins after surgery found that patients who had adjuvant RT to the vulva, groins, and lower pelvis had a lower recurrence rate (Faul et al. 1997). The dose used in this study was 56 Gy, and with close margins, recurrence rates were 30% with no further treatment and 9% with radiation. With positive margins, 69% of patients recurred with no further treatment versus 39% with adjuvant RT. Viswanathan et al. published a retrospective study also showing high rates of recurrence with close and positive margin. They had found that patients who had received an adjuvant RT dose to >=56 Gy had a lower risk of relapse compared to those who received <=50.4 Gy.

5.2 Advanced Stage Vulvar Cancer

5.2.1 Preoperative Chemoradiation and Definitive Treatment

Locally advanced vulvar cancer can be challenging for treatment as patients present with disease encroaching or invading midline structures such as the anus, urethra, or vagina. These patients are typically considered for an aggressive surgical approach such as pelvic exenteration with the goal of achieving a complete resection. Definite radiation or chemoradiation had previously not been considered a common approach in vulvar cancer due to poor outcomes and significant acute toxicities (Iversen 1982). However, published data had gradually emerged showing promising results with chemoradiation in a definitive or preoperative setting (Hacker et al. 1984). Based on this, the GOG conducted prospective studies to evaluate chemoradiation for vulvar cancer.

In the phase II study by Moore et al., 73 patients with stage III–IV primary cancers were enrolled for chemoradiation treatment with a planned split course with break followed by surgical excision of residual disease and groin dissection (Moore et al. 1998). Radiation was delivered to a dose of 4760 cGy. With this relatively low dose of radiation, 34 (48%) of patients were found to have a complete clinical response (cCR). Three of these patients did not go on for planned surgery, but of the remaining 31, 22 (70%) had a complete pathological response (pCR). A parallel study by the GOG evaluated preoperative chemoradiation for patients with N2/N3 nodal disease (Montana et al. 2000). Again, a dose of 4760 cGy with concurrent chemotherapy was given, and 41% of patients who went for resection (95%) had a pCR after inguinal node dissection.

From the results of the GOG studies, it is evident that chemoradiation has a role in the treatment of vulvar cancer. Definitive chemoradiation is increasingly used in this setting with no resection planned if a clinical complete response is achieved (Montana et al. 2000; Akl et al. 2000). In the GOG 205 study, patients were treated with chemoradiation consisting of weekly cisplatin and a total dose of 5760 cGy. It was found that 64% of patients achieved a complete clinical response, and from surgical biopsy, 78% had a pCR. Therefore, radiation may be a primary treatment options for locally advanced patients when dose is escalated to treat gross disease.

Advanced techniques may help in limiting toxicities associated with high-dose RT to the perineum and pelvis.

An area of debate in definitive RT is the ability of radiation to adequately treat microscopic nodal disease. A GOG study randomized patients with clinically negative groins to RT versus groin dissection. The trial was stopped after interim analysis as there were a high number of failures in the RT arm. However, it was found on analysis that this may have been due to inadequate dose to the nodes as the RT was prescribed to a depth of 3 cm. The average depth of the inguinofemoral nodal region is found to be approximately 6 cm and can be as high as 17 cm on CT imaging analysis (Koh et al. 1993). The Dutch Gynecology Oncology Group is also studying radiation for microscopic nodal disease in the GROINSSV-II observation trial. In this study, patients with positive sentinel lymph nodes are treated with radiation without further nodal dissection.

5.2.2 Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is a technique that achieves a conformal dose of radiation using multiple beams that can be modulated spatially and temporally. IMRT is increasingly being used in other gynecologic sites such as postoperative endometrial and cervical cancer. The advantage of IMRT in vulvar cancer is the ability to spare bladder, bowel, and the pelvic bones (Beriwal et al. 2006). However, the concern regarding this approach is suboptimal treatment by missing disease due to challenges in contouring target volumes on CT. A study by Beriwal et al. showed that the mean volume to organs at risk (rectum, bowel, and bladder) excess of 30 Gy was reduced in IMRT versus a three-dimensional conformal technique. In this 30-patient study, 2 patients recurred in the field and another 2 had recurred outside the field. No patients had grade 3 toxicities.

Some of the concerns regarding recurrences are around the conformal volumes targeted with IMRT and contouring of the target structures. A study of preoperative IMRT radiation for locally advanced disease includes a target volume of the lower common iliac, external and internal iliac, and inguinofemoral nodes along with the entire vulvar region (Beriwal et al. 2013). Expansions of 1 cm were made around the vessels except in the inguinofemoral regions were 2 cm was used. A CTV expansion of 1 cm around gross disease was used for the vulva. It should be noted that a 1 cm expansion was added inferiorly beyond skin to account for swelling during treatment and a virtual bolus was placed in the radiation plan that was used during treatment. Besides these studies, IMRT contouring for vulva has not been widely published, and there is currently no established international consensus. With further advancement in radiation delivery techniques and imaging, research into IMRT will play an important role in the treatment of vulva cancer and should be studied with carefully designed protocols.

6 Ovarian Cancer

Epithelial ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system (Siegel et al. 2014). Treatment for this cancer has been standardized to include maximal cytoreductive surgery with staging followed by adjuvant chemotherapy in most cases (NCCN 2015). The role of radiation in the adjuvant setting is controversial, and the NCCN guidelines categorically exclude it as a treatment modality. The rationale for using whole abdominopelvic radiation therapy is the unique pattern of dissemination of ovarian cancer compared with other solid tumors. Though radiation has been shown to be effective as an adjuvant therapy in the early chemotherapy era (Dembo 1984), significant toxicity can be associated with this treatment using 2-dimensional techniques (Schray et al. 1986).

More recently, a role for adjuvant radiation in ovarian cancer has been highlighted in the post-chemotherapy situation in a few series and randomized trials. In a prospective randomized trial, Sorbe et al. for the Swedish-Norwegian Ovarian Cancer Study Group (Sorbe 2003) evaluated consolidation treatment with radiotherapy (20 Gy whole abdomen + 20 Gy lower abdo-pelvic boost)

or chemotherapy (six courses of consolidation chemotherapy–cisplatin 50 mg/m^2 and doxorubicin50 mg/m^2 or epirubicin 60 mg/m^2) in a series of 172 patients with epithelial ovarian carcinoma, FIGO stage III, with complete surgical remission after primary cytoreductive surgery and induction chemotherapy. In the subgroup with complete surgical and pathologic remission, progression-free survival was significantly ($p=0.032$) better in the radiotherapy group (56 % at 5 years) than in the chemotherapy group (36 % at 5 years) and the untreated control group (35 % at 5 years). Overall survival was also most favorable in the radiotherapy group (69 % at 5 years). The number of recurrences was lowest in the radiotherapy group.

Treatment-related side effects were seen most frequently in the radiotherapy group. Late intestinal radiation toxicity of a severe type (obstruction) was recorded in 10 %. This would detract from the use of radiation therapy; however, these could perhaps be reduced with modern methods like IMRT to spare the small bowel (Mahantshetty et al. 2012; Duthoy et al. 2003). A similar study by a French group showed identical benefits but was nonrandomized (Petit et al. 2007).

There is an emerging role for tumor-directed involved field radiation therapy (IFRT) in localized recurrences of ovarian cancer. 50–70 % of patients with advanced ovarian cancer experience recurrences (Hall and Rustin 2011), of which a number present with predominantly locoregional recurrence. Radiation therapy is cancericidal in ovarian cancer and has been shown to be active even in platinum-resistant tumors (Gelblum et al. 1998; Cmelak and Kapp 1997). Several series have shown an impressive locoregional control with IFRT (Albuquerque et al. 2005; Lee et al. 2011). There is a trend towards higher in-field control rates for smaller tumors (Yahara et al. 2013) and for patients undergoing secondary cytoreduction (Albuquerque et al. 2005) (>85 % compared to 50–70 % for primary IFRT) though the lower control rates were probably related to lower total radiation dose in the primary IFRT patients. Most recently a large institutional series did not show a significant benefit for cytoreduction (Brown et al. 2013). In conclusion, IFRT has a place in localized recurrent ovarian cancer and may prolong the chemotherapy-free intervals for these patients. There may be a role for SABR in these situations as a means of maximizing radiation tumor kill.

7 Radiation Techniques

7.1 Stereotactic Ablative Body Radiotherapy (SABR) for Gynecologic Tumors

Image-guided hypofractionated radiation treatment is a new therapeutic paradigm for treating localized tumors outside of the central nervous system and involves delivering very high doses of focused radiation using unique beam arrangements and special immobilization equipment (Uematsu et al. 2001). Translation of brain stereotactic radiosurgery (SRS) principles to extracranial sites has been called stereotactic ablative body radiotherapy (SABR); here, total radiation dose is divided into 3–5 fractions, still with fairly large dose per fraction (6–10 Gy), attempting to decrease adjacent normal tissue toxicity. As already demonstrated in lung and liver cancers, these treatments offer hope for improved local control of cancers that may translate into gains in survival especially for smaller early stage lesions (Timmerman et al. 2010). Translation of the stereotactic radiosurgery and radiotherapy concepts to extracranial sites has not been straightforward. Inherent motion, such as the heart beating, lungs expanding and emptying, and bowels churning, results in movement of potential targets. In addition, the external surface anatomy does not have structures amenable to rigid fixation to a frame. However, these techniques have been applied to the pelvic region, for the treatment of prostate cancer which has a similar anatomic profile to bulky cervical cancer albeit the latter involves a slightly larger volume of treatment (Boike et al. 2011).

A recent comprehensive literature review (Long et al. 2014) of SABR for gynecologic tumors between 1993 and 2013 identified 12 case series and one phase 2 trial (Kunos et al. 2012). This phase II clinical trial evaluated the safety

and efficacy of SABR in 50 patients with recurrent cervical, endometrial, ovarian, and vulvar cancer. SRS was used to deliver 24 Gy in 3 fractions to a clinical target volume (CTV) that included the gross tumor volume (GTV) as well as surrounding fluorodeoxyglucose (FDG)-avid areas. Sixty-two percent of patients showed clinical benefit at 6 months. Most toxicity was mild, though one patient did experience grade 4 hyperbilirubinemia and another developed an enterovaginal fistula. SABR was considered safe for recurrent gynecologic tumors by the authors.

7.1.1 Cervical Cancer

There is limited experience in the literature utilizing image-guided hypofractionated radiation treatment for primary cervical cancer. Most of the series are for recurrent or persistent gynecologic tumors in pelvis or retroperitoneum (Mollà et al. 2005; Mayr et al. 2011; Bignardi et al. 2011; Guckenberger et al. 2010; Higginson et al. 2011). These have been successful as an alternative to brachytherapy with comparable toxicity. For primary cervical cancers, while intracavitary brachytherapy provides the best results, there are a group of patients unable to have standard brachytherapy for whom pilot studies of image-guided hypofractionated radiation treatment have been performed (Mollà et al. 2005; Hsieh et al. 2010; Kubicek et al. 2013; Haas et al. 2012). These have been able to demonstrate in small patient samples that image-guided hypofractionated radiation treatment for cervical cancer can be delivered safely in the clinic, but systematic follow-up and longer-term local control data are unavailable in some of the recently published studies.

7.1.2 Endometrial Cancer

One approach has been to replace vaginal cuff brachytherapy with a stereotactic radiation boost (Demiral et al. 2013). This is strictly not classified as ablative therapy. SABR has also been reported as a substitute for brachytherapy in patients with primary endometrial cancer. In an interesting approach by Mollà et al. (2005), in the 4 nonoperated patients with primary uterine cancer after 45 Gy external pelvic radiation, a dose of 4 Gy/fraction in 5 fractions with 2–3 days' interval was delivered. Patients were immobilized in a customized vacuum body cast and optimally repositioned with an infrared-guided system developed for extracranial SRT. To further optimize daily repositioning and target immobilization, an inflated rectal balloon was used during each treatment fraction. CT resimulation was performed before the last boost fraction to assess for repositioning reproducibility. At 12-month median follow-up, no recurrences were reported for the endometrial cancer group. Mostly grade 1 or 2 toxicities were noted.

7.1.3 Recurrent Cancer

There is an emerging role of SABR in managing recurrences of endometrial and cervical cancer, particularly with the history of previous radiation and where brachytherapy cannot be easily administered (e.g., pelvic side wall recurrences). In a series by Seo et al. (2014), 23 patients with locally recurrent cervical cancer limited to the pelvic sidewall were treated with SBRT dose ranged from 27 to 45 Gy (median, 39 Gy) in three fractions. The 2-year overall survival, local progression-free survival and disease progression-free survival rates were 43 %, 65 %, and 52 %, respectively. Patients with small tumors (gross tumor volume <30 cm^3) had a significantly longer 2-year overall survival rate and 2-year local progression-free survival rate than did patients with large tumors (overall survival rate: 89 % vs 12 %; $P=0.0001$ and local progression-free survival: 85 % vs 0 %; $P=0.0199$). There was a 13 % incidence of severe toxicity, but 70 % patients achieved analgesic (nonsteroidal anti-inflammatory drug or narcotic) reduction of 50 % or more from baseline. However, SBRT should be used carefully in the treatment of large tumors, as the incidence of severe late toxicity increases with the size of the tumor. Other smaller series have been published with good results (Guckenberger et al. 2010; Deodato et al. 2009). Oligometastatic disease in abdominal and particularly retroperitoneal regions can be targeted effectively by SABR depending upon location. Due to the conformal nature of SBRT, it cannot be used for micrometastatic disease effectively, but it can be an effective

tool in managing visible recurrent isolated PALN disease especially since it allowed higher doses with less toxicity. Choi et al. enrolled 30 patients with isolated PALN metastases originating from uterine cervical and corpus cancer who had received SABR. All patients were shown to have isolated PALN metastases by computed tomography (CT) and/or positron emission tomography (PET)–CT. The 4-year OS rate was 50.1 %, and the median survival time was not reached (Choi et al. 2009). The suggestion is that SABR could benefit patients with pelvic or para-aortic node recurrences who are not candidates for exenteration or salvage radiotherapy; however, further studies are needed to confirm these results.

Conclusion

We have described areas of progress and controversy regarding the role of radiation therapy in the management of gynecologic cancers. This is an ever-evolving process and the results of new clinical trials in endometrial cancer will define its future role in that site. The development of precise image-guided adaptive brachytherapy technology has revitalized its place in advanced cervical cancer. Cutting-edge stereotactic and intensity-modulated radiation delivery technologies have enabled the use of radiation in previously exempt situations for recurrent gynecologic cancers. In the future, the use of particle therapy with protons and carbon may define new paradigms for the use of radiation therapy for female cancers.

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Head and Neck Cancer

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Abstract

Head and neck radiotherapy is a continuously evolving field. The disease itself has changed with the increase in human papilloma virus (HPV) associated oropharyngeal cancer. With this new disease entity, oncologists are struggling to determine optimal therapy. As radiation oncologists, we are questioning our traditional use of chemotherapy as well as our radiation doses and volumes.

1 Introduction

Head and neck radiotherapy is a continuously evolving field. The disease itself has changed with the increase in human papilloma virus (HPV) associated oropharyngeal cancer. With this new disease entity, oncologists are struggling to determine optimal therapy. As radiation oncologists, we are questioning our traditional use of chemotherapy as well as our radiation doses and volumes.

While there has been little change in the incidence or biology of larynx cancer, there has been

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recent concern regarding the best overall care for locally destructive tumors. With the use of chemotherapy to bioselect for organ preservation and the improved larynx preservation seen with concurrent chemoradiation, there has been a sweeping adoption of chemoradiation for all locally advanced larynx patients. We will review the challenge of proper utilization of organ preserving chemoradiation compared with laryngectomy for overall patient outcomes, including survival.

One constant in head and neck radiotherapy is its morbidity. Still, practitioners search for agents to reduce both acute and long-term side effects including mucositis and xerostomia. We will review controversies regarding these agents as well as therapies for osteoradionecrosis. Many of these patients require feeding tube placement. We will review the controversy of prophylactic placement versus placement as needed.

Finally, as a technology-based specialty, radiation oncologists are continuing to explore the use of particle therapy in the management of head and neck cancer. We will review this topic with special attention to proton therapy, heavy ion, and neutron therapy.

2 Induction Chemotherapy

2.1 Induction Chemotherapy Is Dead

Five years ago, there was no greater controversy in head and neck radiotherapy than the question of the value of induction chemotherapy compared with chemoradiotherapy alone for locoregionally advanced head and neck cancer. The exciting results of TAX 324 showed improved 3-year survival (62% vs. 48%) when docetaxel was added to cisplatin and fluorouracil as induction chemotherapy in 501 patients with stage III/IV head and neck cancer (Posner et al. 2007).

However, since TAX 324, two large randomized phase III trials comparing induction chemotherapy followed by chemoradiation versus concurrent chemoradiation alone have failed to show a benefit in overall survival. PARADIGM was a multicenter, randomized phase III trial evaluating induction chemotherapy with three cycles of docetaxel, cisplatin, and fluorouracil (TPF) followed by concurrent chemoradiotherapy with either docetaxel or carboplatin compared with concurrent chemoradiotherapy alone (radiation with two cycles of cisplatin) (Haddad et al. 2013). This study only enrolled 145 patients with stage III/IV disease over 4 years. It failed to show a significant benefit to induction chemotherapy with 3-year survival of 73% compared with 78% in the chemoradiation alone arm (Fig. 1). Febrile neutropenia was more common in the induction chemotherapy group.

Shortly after the results of PARADIGM, another negative study comparing induction chemotherapy followed by chemoradiation versus chemoradiation alone was published in 2014. The DeCIDE (Docetaxel-based Chemotherapy plus or minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer) trial was a randomized phase III trial of 285 patients with N2 or N3 nodal disease (Cohen et al. 2014). Here, patients received either chemoradiation alone (docetaxel, fluorouracil, hydroxyurea every other week plus 150 cGy BID to 74–75 Gy) or two 21-day cycles of induction chemotherapy (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and fluorouracil 750 mg/m^2 on days 1–5) followed by the same chemoradiation. At a median follow-up of 30 months there was no statically significant difference in overall survival, relapse-free survival, or disease-free survival.

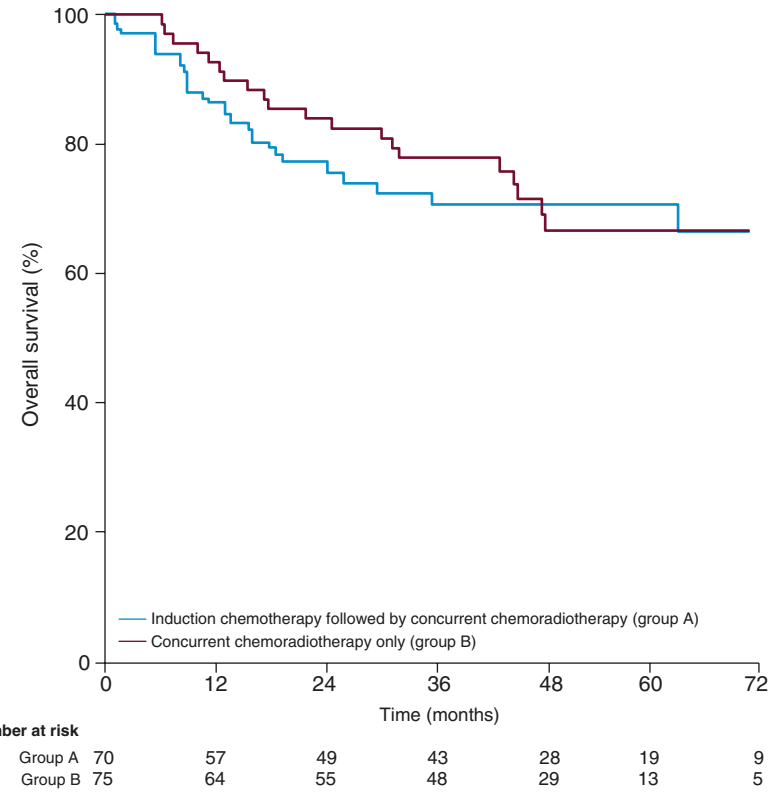


Fig. 1 PARADIGM Kaplan–Meier overall survival. Figure courtesy: Haddad et al. Lancet Oncol 2013;14: p 260 (Haddad et al. 2013)

2.2 Induction Chemotherapy: A Historic Perspective

While induction chemotherapy may not provide improved survival in locally advanced head and neck cancer, there has been significant interest in pursuing its use in bioselection. Wolf et al. didn't set out to improve survival in the VA Larynx trial first published in 1991; the goal was organ preservation (Wolf et al. 1991). Here, patients received two cycles of induction cisplatin and fluorouracil as a means to select patients who could appropriately receive definitive radiation to provide the best chance to preserve the larynx. Patients with either a complete (31%) or partial (54%) response to induction chemotherapy went on to receive a third cycle of chemotherapy followed by definitive dose radiation. The control arm in this study was treated with upfront surgery with total laryngectomy followed by post-operative radiation. Survival was not compromised by this organ preservation approach with 68% survival at 2 years in both study arms. Using induction chemotherapy to select the appropriate patients allowed for larynx preservation in 64%. The EORTC 24891 study also used induction chemotherapy to achieve laryngeal preservation in patients with hypopharynx and larynx cancers (Lefebvre et al. 2012). In this study, 202 patients were randomized to either laryngectomy with partial pharyngectomy and neck dissection followed by radiation or to chemotherapy with up to three cycles of induction cisplatin and fluorouracil followed by definitive radiation in those patients achieving a complete clinical response. At a median follow-up of 10.5 years, although survival was poor, it was not compromised by the induction chemotherapy for organ preservation strategy: 13.8% in the surgery arm and 13.1% in the induction chemotherapy arm. Using the induction chemotherapy approach allowed more than half of the surviving patients to retain their larynx (59.5% at 5 years).

2.3 Induction Chemotherapy in the HPV Era

In the last 20 years, there has been a change in the epidemiology of head and neck cancer (Gillison et al. 2000). HPV-associated oropharyngeal cancer has increased in frequency and is now the most common head and neck cancer diagnosed in 2016. Much has been written and much is continuing to be learned about HPV-associated oropharyngeal cancers, but one thing is clear: these tumors have better outcomes when treated with chemoradiation than HPV-negative tumors. Ang et al. performed a retrospective analysis using patients treated on RTOG 0129 showing improved survival in HPV-associated oropharyngeal cancers (Ang et al. 2010). A total of 743 patients were enrolled on RTOG 0129. Of these patients, the majority had oropharyngeal cancers (60.1%). HPV status was known in 74.6%. HPV-positive cancers were more common in the never or low pack-year smokers. Patients with HPV-associated tumors had improved overall survival over their HPV-negative counterparts: 3 year overall survival was 82.4% vs. 57.1%. Progression-free survival was also improved (Fig. 2).

With improved outcomes seen in the increasingly common HPV-associated oropharyngeal cancer, investigators have recently sought to de-intensify therapy to reduce the morbidity of therapy without compromising the excellent outcomes already achieved. The concept of using induction chemotherapy as a way to bioselect patients for treatment de-intensification has been

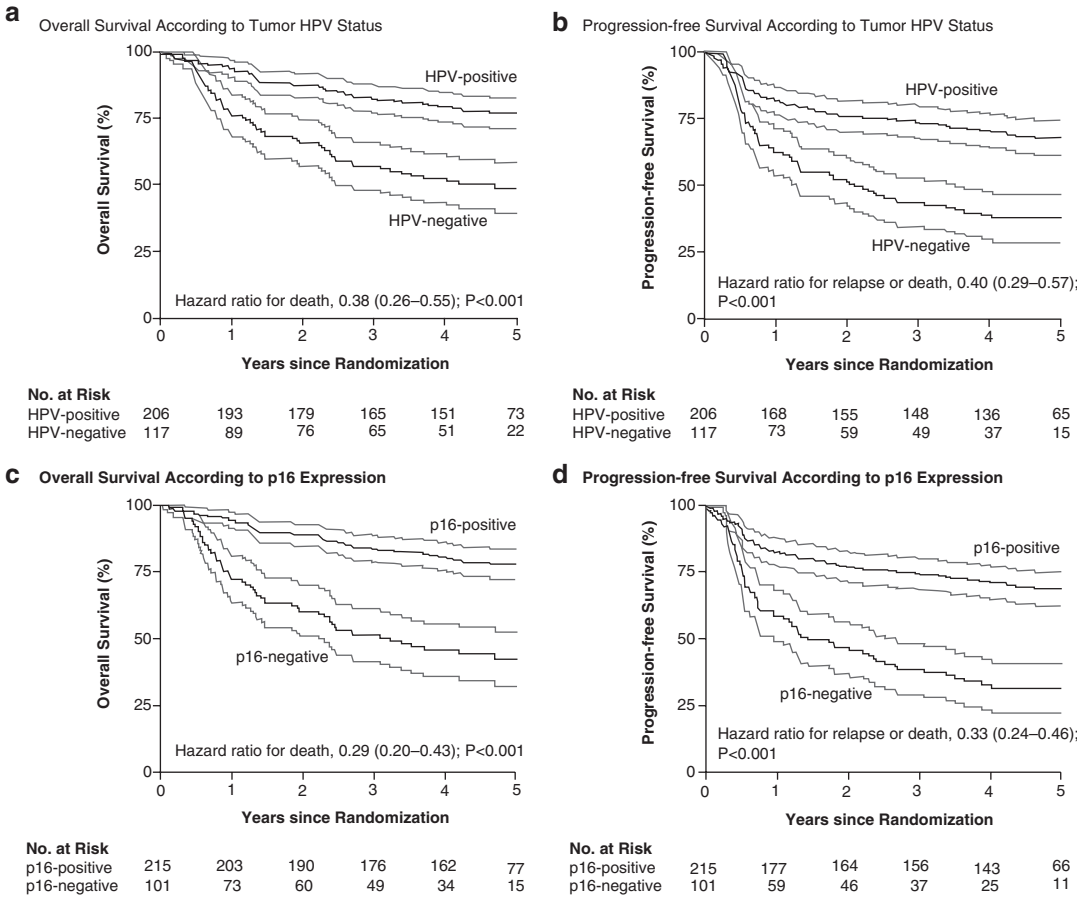


Fig. 2 Kaplan–Meier estimates of survival among the RTOG 0129 study patients with oropharyngeal cancer (**a**) Overall survival according to tumor HPV status. (**b**) Progression-free survival according to tumor HPV status. (**c**) Overall survival according to p16 expression. (**d**) Progression-free survival according to p16 expression. Figure courtesy of Ang et al. NEJM 2010;363: p 30 (Ang et al. 2010)

explored in the HPV-positive population. Results of ECOG 1308 were presented at the 2014 ASCO meeting (Cmelak et al. 2014). Here, patients with resectable HPV + oropharyngeal squamous carcinomas were treated with three cycles of induction cisplatin, paclitaxel, and cetuximab. Most of these patients (71%) had a clinical complete response to induction chemotherapy. These patients then went on to receive reduced dose (54 Gy) intensity-modulated radiation therapy (IMRT) with weekly cetuximab. Using 22% less radiation in this selected group still resulted in 2-year progression-free survival of 80% and overall survival of 93%. As seen in other HPV + series, patients with extensive smoking histories or T4 lesions did less well with this approach. Still, patients with T1–T3, N0–N2b tumors with less than 10 pack-year smoking histories did exceptionally well. In this select group, using induction chemotherapy to select patients to receive 54 Gy instead of 70 Gy, 2-year progression-free and overall survival was an impressive 96%.

The University of Chicago has creatively used an induction chemotherapy approach to select for a different way to de-intensify: response-adapted volume de-escalation (RAVD). Here, patients with locally advanced disease received two cycles of induction cisplatin/paclitaxel/cetuximab with or without everolimus. If patients had a "good response" with at least 50% tumor reduction to induction chemotherapy, they then received concurrent chemoradiation, but the radiation volumes only covered the initial gross disease plus margin. The concept here is that for the good responders, the tumor is chemotherapy-sensitive. It was hypothesized that chemotherapy should sterilize microscopic disease in the regional nodes. The use of chemotherapy to sterilize microscopic carcinoma in regional nodes is extrapolated from lung cancer chemoradiation where omitting elective nodal radiation allows for the use of smaller radiation volumes while not compromising regional control (Rosenzweig et al. 2001). Even in those patients experiencing less than 50% response, these investigators reduced the radiation volume to include only the gross disease and the "next nodal station" for the first 45 Gy before reducing the volume to the gross tumor plus margin (Fig. 3) (Villaflor et al. 2016).

When specifically evaluating their 59 HPV+ oropharynx patients, 30 (51%) experienced a

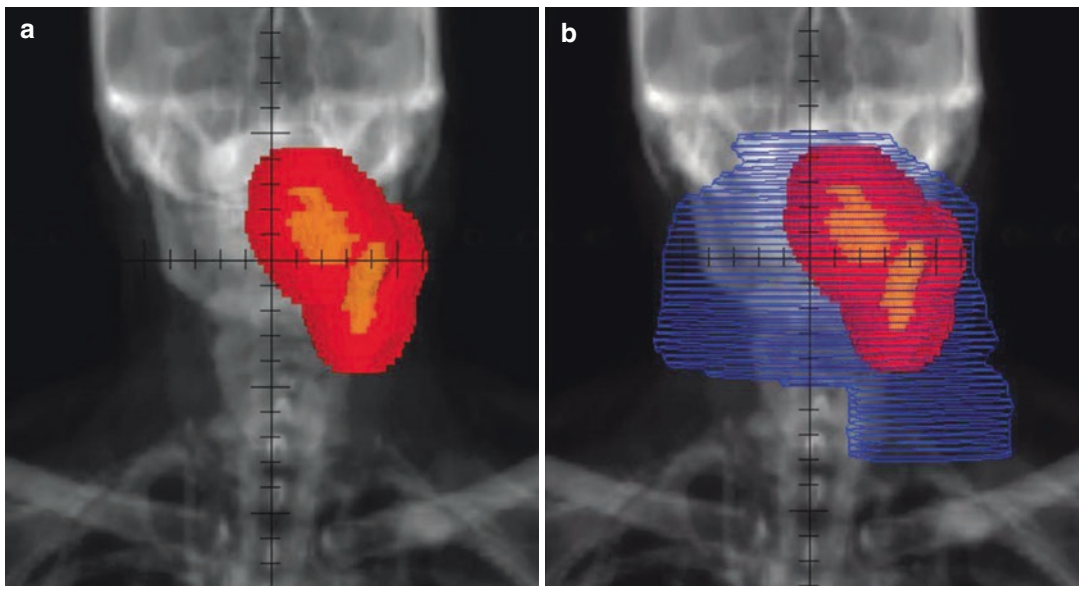


Fig. 3 Radiation treatment planning digitally reconstructed radiograph of a patient with oropharynx cancer and left level II adenopathy. (**a**) Represents a good response to induction chemo and was treated with RVAD, radiation delivered to a single volume to cover gross tumor volume plus 1.5 cm. (**b**) Non-responder to induction chemotherapy, treated with radiation field that includes the next nodal levels, this field is seen in *blue*. Figure courtesy: Villaflor et al. Annals of Oncology 2016;27: p 912 (Villaflor et al. 2016)

good response to induction chemotherapy. Two-year progression-free survival was 93% with overall survival 92%. None of these 30 HPV+ good responders had suffered a locoregional first failure at a median follow-up of 2 years. The authors reported decreased morbidity with this RAVD approach observing reduced gastrostomy tube dependence at 3 and 6 months in the good responders treated with smaller volume radiation.

3 Human Papilloma Virus-Positive Oropharynx Cancer: Dose De-Intensification

As discussed earlier, HPV-associated oropharyngeal cancers do better than their HPV-negative counterparts. These tumors respond better to chemotherapy and to radiation. The concept of increased inherent radiosensitivity in these HPV-related tumors is itself somewhat controversial. Vlashi et al. have reported HPV-positive cell lines having a lower frequency of cancer stem cells than HPV-negative cell lines (Vlashi et al. 2016). This lower number of cancer stem cells inversely correlated with radiosensitivity. Further, HPV-negative cell lines have enhanced ability to undergo radiation-induced dedifferentiation into radioresistant cancer stem cells.

O'Sullivan et al. at Princess Margaret Hospital in Toronto have proposed de-intensifying therapy for HPV-positive oropharynx cancer patients by using recursive partitioning analysis (RPA) to segregate HPV-positive patients into those with low and high risk for distant spread (O'Sullivan et al. 2013). In their analysis of 505 patients, HPV-positive T1–T3, N0–N2a and N2b patients with less than 10 pack-year smoking history had low risk of experiencing distant failure. These authors felt these low risk patients would be the best candidates for de-intensifying strategies.

Using concurrent cetuximab instead of cisplatin with IMRT has been explored as a de-intensification approach in RTOG 1016. This study has completed with 948 patients accrued. As of July 2016, we await the results of this large study.

Certainly much of the morbidity of head and neck chemoradiotherapy is from the radiation. In fact, most of the long-term effects can be attributed to radiation damage to the microvasculature and the resultant fibrosis. We have previously discussed ECOG 1308, where Cmelak et al. were able to use induction chemotherapy to select patients for lower dose radiotherapy using 54 Gy in good chemotherapy responders vs. 69.3 Gy in poor responders. Again, in this series of 77 patients, 81% were able to receive the lower radiation dose while experiencing an excellent 2-year progression-free survival rate of 80% and 2-year overall survival of 93%. In the select "best case" patients (T1–T3, N0–N2b with less than 10 pack-year smoking history), the 2-year progression-free and overall survivals were both 96%.

Given the lack of survival benefit seen in both the PARADIGM and DeCIDE studies using induction chemotherapy, many providers are more comfortable using treatment strategies with concurrent chemoradiation from the start. In 2015, Chera et al. reported a de-intensification of chemoradiation for select HPV-associated oropharyngeal squamous cell carcinomas (Chera et al. 2015). This small phase II trial included 43 patients with T0–T3, N0–N2c HPV+ cancers. Patients also had minimal smoking histories: less than 10 pack year or if greater than 10 pack year, no greater than 30 pack years and smoking abstinence for at least 5 years. IMRT dose was reduced to 60 Gy and was delivered concurrently with lower dose cisplatin at 30 mg/m^2 per week. The primary endpoint of this study was pathologic complete response based upon biopsies of the original primary site and neck dissection. In this series, the overall pathologic complete response rate was 86% – seen in 37 of 43 patients. Placement of a feeding tube was required in 39% of these patients for a median duration of 15 weeks. Current work from this group out of the University of North Carolina (study LCCC 1413) will utilize follow-up PET scan at 12 weeks post-therapy rather than relying on pathologic confirmation of complete response. Moreover, this follow-up study will further de-intensify therapy by omitting chemotherapy for early stage disease (T0–T2, N0–N1).

NRG oncology seeks to explore the possibility of de-intensification of chemoradiation for select HPV-associated patients in a multi-institutional intergroup trial. Study HN002 is a phase II trial for p16+ non-smoking patients with locoregionally advanced oropharynx carcinomas. Two treatment arms will be compared: chemoradiotherapy and radiotherapy alone. Both arms have reduced intensity. Chemoradiation uses 60 Gy with lower dose chemotherapy with concurrent weekly cisplatin 30 mg/m^2. The radiotherapy alone arm radiation dose is also less at 60 Gy, but it is delivered using an accelerated fashion of six fractions each week over 5 weeks. This study plans to accrue 296 patients with T1–T2, N1–N2b, or T3 N0–N2b disease. Eligible patients must have 10 pack-year or less smoking histories. The primary objective of HN002 is to select the treatment arm with a 2-year progression-free survival rate of at least 85% without unacceptable swallowing toxicity assessed at 1 year post-therapy.

One of the clinical characteristics of HPV-associated oropharyngeal cancers is the presentation with cystic lymphadenopathy, which can be quite large while still having small primary tumors. In fact, the incidence of cervical squamous cell carcinomas of unknown primary has been increasing in the HPV era. Coinciding with this change in oropharyngeal tumor biology, surgical technology has evolved. Transoral robotic surgery (TORS) has become a viable surgical option to resect these small oropharyngeal primaries. This technique allows resection without requiring mandibulotomy to gain exposure. Since these primary tumors tend to be smaller, most surgical beds can heal without requiring grafts or microvascular flaps. Most importantly, results using TORS for select early stage tumors have been outstanding. With a median follow-up of 17 months, the University of Pennsylvania reports only 3.3% 2-year locoregional failure rate in 114 HPV+ oropharyngeal cancer patients treated primarily with TORS and neck dissection (Kaczmar et al. 2016). Continuing with the theme of de-intensifying therapy in HPV+ oropharyngeal cancers, ECOG 3311 is evaluating less intense adjuvant therapy after TORS and neck dissection for select patients (clinical T1–T2, N1–N2b tumors). The primary study question is whether post-operative radiation dose can safely be reduced from 60 Gy to 50 Gy in "intermediate risk" patients. Pathology must show negative (but less than 3 mm) surgical margins but includes high risk findings including perineural invasion, lymphovascular invasion, two to four metastatic nodes, and even nodes with minimal extracapsular spread (less than 1 mm). High risk patients with positive surgical margins, greater than 1 mm extracapsular nodal spread or five or greater involved lymph nodes still receive post-operative chemoradiation with 66 Gy over 33 fractions combined with weekly cisplatin 40 mg/m^2. Interestingly, low risk patients with T1–T2, N0–N1 disease undergo observation only with no adjuvant therapy for this favorable group. As of April 2015, 135 patients have enrolled in this important study of adjuvant care in the post-TORS setting.

4 Decreasing Radiation Treatment Volume

Of course, de-intensifying therapy doesn't just have to mean lowering the dose of radiation and chemotherapy. Reducing the volume of tissue irradiated can also lessen both acute and long-term morbidities of therapy.

One of the first examples of successfully reducing radiation treatment volumes actually pre-dates the IMRT era. The concept of sparing the contralateral neck when treating early tonsil cancers was introduced by Murthy and Hendrickson (1980). Jackson et al. first reported successful outcomes using ipsilateral radiation for early stage tonsil cancer in 1999 (Jackson et al. 1999). O'Sullivan et al. reported the Princess Margaret experience using ipsilateral radiotherapy techniques in 228 patients treated from 1970 to 1991 (O'Sullivan et al. 2001). Tumor location was important with lesions involving 1 cm or less of the "ipsilateral hemistructure" of the soft palate or tongue base (Fig. 4). Most (91%) of these patients were treated using wedge pair photon technique. In this large series, the total rate of contralateral nodal failure was only 3.5%.

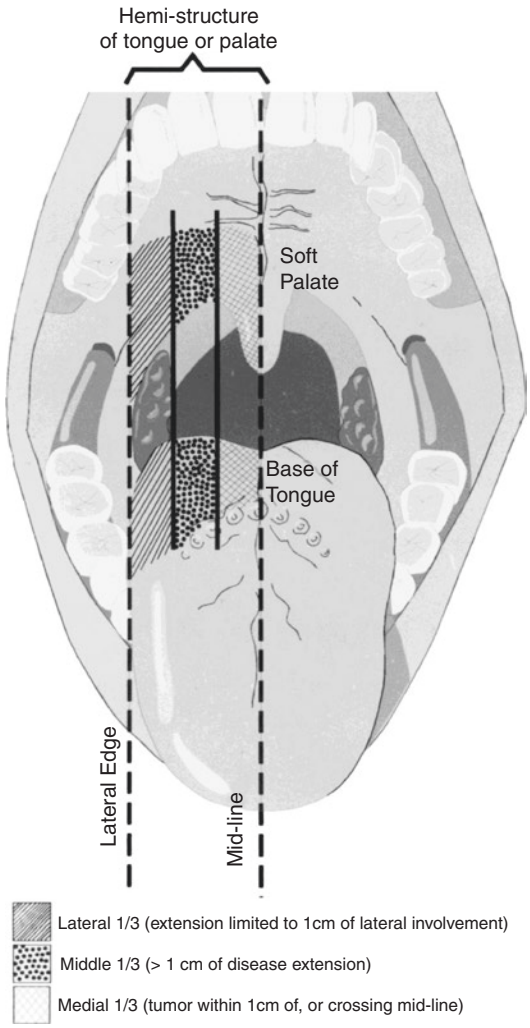


Fig. 4 Schematic of the lateral, middle, and medial hemi-structure involvement based on tumor location and extent of disease within the base of tongue and soft palate from the lateral edge of the tonsillar region to midline. Courtesy O'Sullivan Int J Radiat Biol Phys 2001;51: p 334 (O'Sullivan et al. 2001)

No patient with an N0 neck or a T1 primary tumor failed in the contralateral neck. MD Anderson has more recently published their experience with unilateral radiotherapy for tonsil cancer (Chronowski et al. 2012). In their experience of 102 patients, disease was limited to the tonsillar fossa or anterior tonsillar pillar with less than 1 cm involvement of the soft palate. Patients with any base of tongue involvement were excluded in this series. Most (67%) patients were treated using IMRT. Also, most (65%) had node positive disease with 42% having N2a or N2b necks. Even given the high incidence of positive ipsilateral adenopathy, only two patients suffered contralateral neck failure. Five-year freedom from contralateral nodal recurrence was 96%. In 2012, the American College of Radiology published "appropriateness criteria" for the use of ipsilateral radiation for tonsil cancer (Yeung et al. 2012). The following statements regarding appropriate patient selection for ipsilateral radiation were made: (1) The extent of soft palate or base of tongue invasion should be less than 1 cm. If the extension is 1 cm or greater, bilateral neck irradiation is recommended; (2) Bilateral neck irradiation is recommended for nodal stages N2b or higher; (3) There is "insufficient data at this time to alter treatment decisions based on HPV status". Patients should receive ipsilateral neck irradiation based upon the extent of the primary toward midline and the amount of ipsilateral nodal disease "regardless of the patient's HPV status."

Certainly, one key to decreasing the volumes irradiated in the IMRT era is to have a better understanding of the nodal regions at significant risk for microscopic spread of disease. Kjems et al. have recently questioned the need for routine irradiation of retropharyngeal and submandibular nodes in head and neck radiotherapy (Kjems et al. 2016). In this review from Denmark, 942 patients with oropharyngeal, hypopharyngeal, laryngeal, and oral cavity cancers were treated with primary radiation. The retropharyngeal region was only "routinely" irradiated in patients with tumors invading the posterior pharynx. The submandibular region (level IB) was only treated in cases that involved the oral cavity. Most (77%) of these patients were treated using IMRT. Seven hundred had treatment plans available for review. Of these only two (0.2%) recurred in the retropharynx and only seven (1%) failed in level IB. Since these recurrences were so uncommon, the authors conclude "restricting elective irradiation of the upper retropharyngeal region to cases with involvement of the posterior pharyngeal wall and level IB to cases involving the oral cavity is safe."

The challenge then comes in trying to adequately irradiate level IIA, the primary nodal drainage so frequently involved in oropharyngeal cancers while still meaningfully sparing IB and the submandibular gland. IMRT planning and delivery can only do so much in sparing adjacent critical normal tissues. The first step may be to better understand the radiation tolerance of the submandibular gland. Fortunately, the University of Michigan has performed this work (Murdoch-Kinch et al. 2008). This group evaluated 148 head and neck cancer patients before receiving IMRT and then followed them throughout treatment and for 2 years after radiation. Measurements of unstimulated and stimulated submandibular flow rates were performed. Both flow rates appeared to recover after radiation doses up to a threshold of 39 Gy.

As discussed earlier, perhaps we can apply the concept of chemotherapy to sterilize microscopic disease in regional nodes used in treating non-small cell lung cancer to head and neck cancer. The University of Chicago has certainly challenged our conventional beliefs of appropriate radiation target volumes with their Response-Adapted Volume De-Escalation (RAVD) based upon tumor response to induction chemotherapy. This may be even more relevant in the HPV era.

5 Chemoradiation Vs. Laryngectomy Plus Adjuvant Therapy for Locally Advanced Laryngeal Cancer

With all the morbidities and fears that head and neck cancer and its treatment carry for our patients, total laryngectomy may be the most dreaded. We have already discussed the historic perspective of using induction chemotherapy to select appropriate patients for laryngeal organ preservation in the VA Larynx trial and in the European EORTC 24891 trial for hypopharyngeal and laryngeal tumors.

RTOG 9111 sought to improve outcomes in patients with locoregionally advanced larynx cancer. This trial consisted of three arms: radiation alone, induction chemotherapy followed by radiation as used in the VA Larynx trial, and radiation with concurrent chemotherapy (three cycles of cisplatin 100 mg/m^2 every 3 weeks during radiation) (Forastiere et al. 2013). Median follow-up of greater than 10 years with over 500 patients analyzed appears to favor the concurrent cisplatin and radiation arm of the study. While locoregional control and laryngeal preservation were significantly better in the concurrent chemoradiation arm over induction chemotherapy or radiation alone, this therapy failed to improve overall survival. Concurrent cisplatin and radiation resulted in an outstanding 88% laryngeal preservation rate at 2 years. Combined chemoradiation resulted in a 54% relative reduction in risk of laryngectomy compared with radiation alone and a 42% reduction compared to induction chemotherapy followed by radiation. Still, larynx preservation did not translate into improved overall survival. Ten-year survival is only 28% in the concomitant arm, not significantly different than 39% seen in the induction arm or 32% after radiation alone. Exploratory analysis has been performed regarding the cause of death: from larynx cancer or "death not caused by study cancer" (Fig. 5). At 10 years, the concurrent radiation and cisplatin arm has a significantly *worse* rate of survival in the analysis of those "deaths not related to larynx cancer": 52.8 vs. 69.8% in the other arms ($p = 0.03$). Although this study failed to report increased late toxicity or worse speech/swallowing function after concurrent chemoradiation, this increase in deaths unrelated to larynx cancer is troubling. Olsen, an otolaryngologist from the Mayo Clinic has postulated that concurrent chemoradiation results in increased atherosclerosis of the carotids leading to stroke and delayed but increased pharyngeal fibrosis and stenosis leading to aspiration and pneumonia (Olsen 2010).

Could it be possible that we are under-utilizing laryngectomy? After all, isn't the key to organ preservation *appropriate patient selection*? For large destructive tumors, does organ preservation really make sense when there is not enough remaining larynx to preserve speech and maintain adequate swallowing function? Grover et al. from the University of Pennsylvania specifically

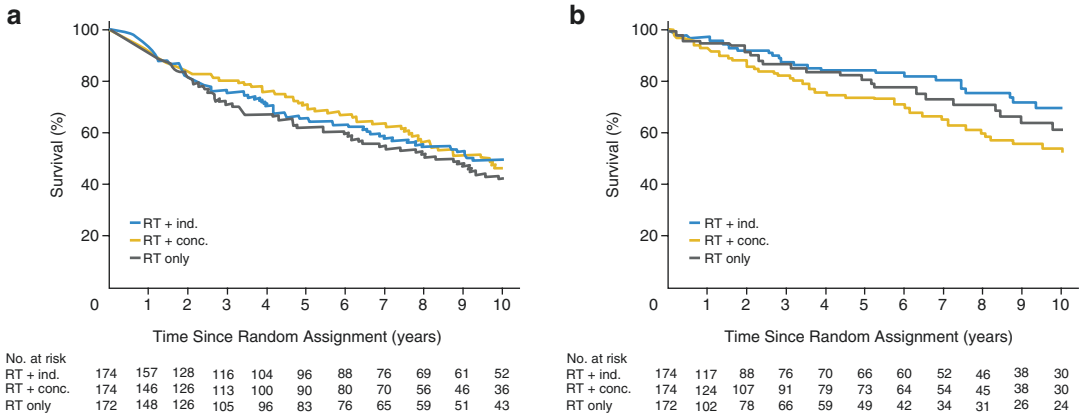
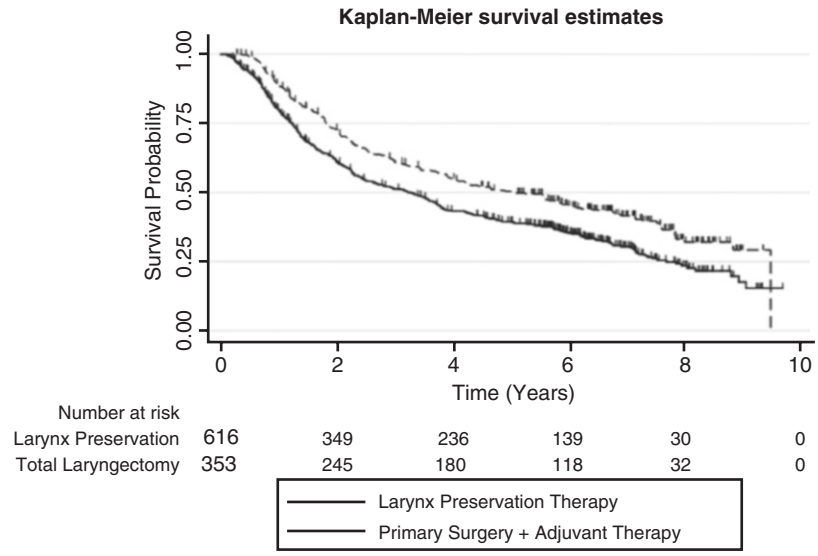


Fig. 5 RTOG 9111 Kaplan–Meier overall survival curves separated by (**a**) deaths from laryngeal cancer (**b**) deaths not caused by laryngeal cancer. Figure courtesy of Forastiere et al. J Clin Oncol 2012;31: p 850 (Forastiere et al. 2013)

Fig. 6 Kaplan–Meier overall survival comparing laryngectomy and adjuvant therapy to laryngeal preservation in T4a tumors. Figure courtesy of Grover et al. Int J Radiat Biol Phys Oncol 2015;92: p 599 (Grover et al. 2015)



evaluated patterns of care and outcomes of 969 larynx cancer patients with T4a disease using the National Cancer database (Grover et al. 2015). Although national guidelines recommend upfront laryngectomy for T4a larynx cancer, this review found most (64%) patients being offered larynx preservation therapy. Interestingly, at "high case volume" facilities, patients were more likely to be treated with laryngectomy. For these patients with locally advanced tumors, survival was significantly better if they were treated with upfront laryngectomy (Fig. 6). Median survival was 61 months after laryngectomy compared with 39 months after upfront laryngeal preservation ($p < 0.001$). While trying to preserve the larynx, we must consider how our treatment choice may affect overall survival. Again, appropriate patient selection is vital.

6 Supportive Care

Technological advances such as image guided radiotherapy, intensity-modulated radiotherapy, and adaptive radiotherapy have had a profound effect on head and neck radiotherapy delivery.

While this has certainly had an impact on acute and chronic adverse events, treatment related morbidity continues to persist. We continue to search for agents to help mitigate the acute and chronic side effects of head and neck radiotherapy and attempt to optimize supportive care and treatment approaches.

6.1 Xerostomia

Xerostomia and mucositis are common adverse effects of head and neck radiation therapy. Ionizing radiation results in the formation of free radicals that damage the DNA. Thiol-containing agents, such as cysteine, are well known to have radioprotective activity (Patt et al. 1949). The necessity to provide preferential protection to normal tissue leads to the development of amifostine (WR-2721) (Kouvaris et al. 2007). Amifostine is a pro-drug that needs to be activated by membrane bound alkaline phosphatase to scavenge free radicals. Concentration of alkaline phosphatase is low in tumors, which provides a selective mechanism for normal tissue protection. Amifostine is also preferentially taken up in the salivary glands and kidneys (Rasey et al. 1986) and has been investigated in normal tissue protection for radiation and chemotherapy.

Brizel et al. reported on a phase III, multi-institutional, randomized trial of the addition of amifostine to post-operative head and neck radiotherapy in which greater than 75% of the both parotids were planned to receive at least 40 Gy. Amifostine reduced grade two and greater acute xerostomia from 78% to 51% and grade two and greater chronic xerostomia from 57% to 34%. Median saliva production was greater with amifostine, 0.26 g v 0.10 g. The use of amifostine had no deleterious effect on tumor control or survival (Brizel et al. 2000). Amifostine use in combination chemoradiotherapy is even more controversial with some trials showing benefit (Vacha et al. 2003; Antonadou et al. 2002), and others failing to do so (Buentzel et al. 2006; Haddad et al. 2009). In addition to the conflicting results from clinical studies, amifostine has other barriers to its routine clinical use. Amifostine is logistically challenging to dose as it has a relatively short bioavailability and must be delivered within a short time before daily radiotherapy. In addition to the financial cost of this medication, it is associated with significant side effects including nausea and hypotension. The benefit of amifostine in reducing radiation xerostomia is further challenged in the IMRT era where salivary gland sparing is routine (Nutting et al. 2011; Kam et al. 2007). In fact, Rudat et al. have retrospectively compared parotid function using quantitative salivary gland scintigraphy in those patients receiving conventional non-salivary sparing radiotherapy with amifostine versus IMRT with salivary sparing technique. In their review, the ability for IMRT to spare long-term parotid function was greater than that seen with amifostine using conventional radiation techniques (Rudat et al. 2008).

Cholinergic agonists (e.g., pilocarpine, cevimeline) have effects on exocrine glands to stimulate secretions such as sweat and saliva. These agents are FDA approved for the treatment of radiation-induced xerostomia. They have displayed benefits in salivary flow over multiple randomized, double-blind, placebo-controlled, multi-institutional trials (LeVeque et al. 1993; Johnson et al. 1993). The benefit of their use during radiotherapy is less clear. However, a recent meta-analysis of the randomized, controlled data supports its concurrent use in improving non-stimulated salivary flow (Yang et al. 2016). Still, the cholinergic side effects (e.g., sweating, palpations) can be challenging for patients to tolerate. Given these side effects, there has developed an interest in non-pharmaceutical approaches, including acupuncture. Acupuncture has been studied as a therapy to prevent radiation-induced xerostomia in multiple randomized control trials (Pfister et al. 2010; Cho et al. 2008; Blom et al. 1996; Meng et al. 2012). These results are limited with mixed results and small study populations. Individual patients report subjective benefit from acupuncture with little to no morbidity reported in any series.

6.2 Mucositis

Mucositis is a challenging adverse side effect during radiotherapy for head and neck cancer. This can be very painful and limit patients' ability for proper oral intake.

Palifermin is a humanized keratinocyte growth factor that stimulates the growth of cells that line the mouth and intestinal tract. It has an established role in limiting mucositis in patients undergoing hematopoietic stem cell transplantation (Stiff et al. 2006). Its use for prevention of mucositis in head and neck cancer has been investigated in two randomized controlled trials (Henke et al. 2011; Le et al. 2011). Physician quantified mucositis was reduced in both trials; however, patient reported outcomes remained unchanged. There is currently an ongoing phase II multi-institution trial evaluating a superoxide dismutase mimetic agent to reduce mucositis from head and neck chemoradiation. This utilizes pre-radiotherapy infusion of a small molecule that selectively targets the superoxide pathway accelerating conversion of superoxide to hydrogen peroxide. This mechanism is believed to block the large "burst" of superoxide caused by ionizing radiation which is felt to be the initial step in the development of mucositis [https://clinicaltrials.gov/show/NCT02508389. Accessed June 26, 2016].

6.3 Osteoradionecrosis

Osteoradionecrosis (ORN) of the mandible is a painful complication of head and neck radiotherapy that can range from self-limiting mucosal regression and mandible exposure to necrosis of the jaw with fracture requiring surgical intervention. The pathophysiology is poorly understood, but is felt to be caused by radiation fibrosis of the microvasculature (Marx 1983; Delanian and Lefaix 2002). A standard treatment has not been defined and optimal management remains controversial. Agents including pentoxifylline, vitamin E, and clodronate have been studied as therapy. Hyperbaric oxygen therapy has also been evaluated.

Pentoxifylline is a drug developed initially to treat claudication in peripheral artery disease. It has multiple effects on the body including vasodilation and increasing plasticity of red blood cells. It also further inhibits TNF-alpha and human dermal fibroblast production/proliferation and increases collagenase activity. This activity may reduce radiation fibrosis (Delanian et al. 1999). Pentoxifylline has been investigated in combination with vitamin E, an antioxidate that stops production of reactive oxygen species. This combination, along with clodronate, a bisphosphonate, has shown to be safe and effective in a phase II trial (Delanian et al. 2011). The pentoxifylline-tocopherol-clodronate combination (PENTOCLO) was found to be helpful improving refractory ORN in 54 patients treated with prior radiation. However, randomized data on the benefit of these agents is lacking.

Hyperbaric oxygen therapy (HBOT) has been shown to be clinically useful in diabetic ulcers and burn patients. HBOT increases partial pressure of oxygen in the blood, increasing the delivery of oxygen to hypoxic tissue. This increase in oxygen concentration is thought to stimulate capillary angiogenesis (Clarke et al. 2008; Abidia et al. 2003; Gothard et al. 2004). HBOT has been shown to lower the incidence of ORN after dental extractions and has been used as an adjunct to surgical intervention of established ORN in small series (Dhanda et al. 2016; Marx et al. 1985). However, data from ORN96, a prospective, multicenter, randomized, double blind, placebo-controlled trial failed to show a benefit of HBOT. In this study conducted at 12 university hospitals in France, 68 patients with overt osteoradionecrosis of the mandible were randomized to HBOT or placebo with the primary end point 1-year recovery rate from osteoradionecrosis. The study was stopped early due to worse outcome in the HBOT arm (Annane et al. 2004). This study was criticized for the use of controversial inclusion criteria, lack of stratification, and unusual HBOT twice daily regimen (Dhanda et al. 2016). Further, three-quarters of the HBOT patients failed to reach optimal oxygen concentration.

Two randomized prospective multicenter clinical trials (HOPON and DAHANCA-21) in the UK will hopefully provide a more definitive answer regarding the role of hyperbaric oxygen in the management of ORN (Shaw et al. 2011).

6.4 Feeding Tubes: Prophylactic Vs. Reactive PEG Placement

Despite all our improvements in patient care with increased survival and approaches to decrease treatment intensity and radiation volumes, one fact remains clear: head and neck chemoradiation is *HARD*! Many of our patients will require feeding tube placement to get through and subsequently recover from our therapy. So is it better to place percutaneous endoscopic gastrostomy (PEG) tubes in all of our chemoradiation patients upfront or to place selectively only if and when they are required? PEG placement is associated with complications including infection and bleeding. Still, patients often need PEG support urgently at times when they may be neutropenic or thrombocytopenic from therapy.

Fortunately, even if patients need feeding tube placement for support, long-term dependence on gastrostomy tubes appears to be an unusual occurrence in the IMRT era. Setton et al. performed a pooled analysis of gastrostomy tube dependence in oropharynx cancer patients treated with IMRT (Setton et al. 2015). In this multi-institutional review of 2,315 patients, 1,459 received a gastrostomy tube (63%). Of these patients, 52% had prophylactic placement and 48% had "reactive" placement with tubes placed only as needed. Overall, gastrostomy tube dependence was 7% at 1 year and only 3.7% at 2 years. The risk of gastrostomy tube dependence increased with stage of disease: 5.2% for T1–T2, N0–N2 patients compared with 10.1% for T3–T4 or N3 tumors. Advanced age, increased number of smoking pack years, higher nodal stage, and addition of chemotherapy all increased the risk of gastrostomy tube dependence at 1 year (Fig. 7).

Salas led a small (39 patients) randomized trial of prophylactic PEG compared with no prophylactic PEG in patients receiving chemoradiation for unresectable head and neck cancer (Salas et al. 2009). Quality of life was measured using EORTC QLQ-C30 and EORTC H&N 35 questionnaires. These authors found that placing gastrostomy tubes prophylactically improved post-chemoradiation quality of life especially in terms of reducing "speech problems."

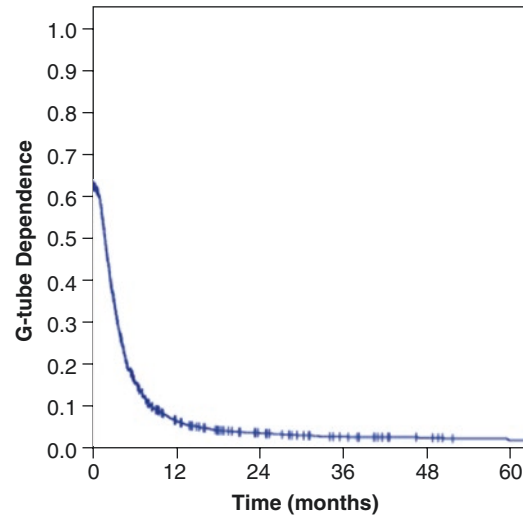


Fig. 7 Gastrostomy tube dependence over time among stage III and IV patients treated with concurrent chemotherapy. Figure courtesy of Setton et al. Cancer 2015;121:294–301 (Setton et al. 2015)

However, prophylactic placement has been associated with greater long-term PEG dependence. In a review of 104 patients receiving chemoradiation for head and neck cancer, Pohar et al. found a higher rate of PEG tube dependence at 1 year (Pohar et al. 2015). Further, 25% of the prophylactic PEG tube patients subsequently required dilation for stricture compared with 13% of the patients who started off eating by mouth. Locher has led a call for a more comprehensive review using evidence-based results on the use of prophylactic PEG tube placement in head and neck cancer (Locher et al. 2011). Her team calls for "more research to inform physician behavior on whether prophylactic PEG tube placement is warranted in the treatment of head and neck cancer." Perhaps, upfront PEG tube placement should be limited to those patients suffering significant pre-treatment weight loss or those patients presenting with severe dysphagia

or odynophagia caused by their cancers. In any case, close involvement of speech therapy early on and throughout treatment is warranted in head and neck cancer patients receiving chemoradiation. These patients should also undergo evaluation and be followed by a registered dietician.

7 Particle Therapies

Particle therapy is a form of external beam radiotherapy that uses beams of energetic ions for cancer treatment. Electrons are small negatively charged particles that can be accelerated close to the speed of light by a standard linear accelerator (Linac) and can be used therapeutically to treat superficial lesions since they have relatively shallow penetration. Electrons are commonly used in daily clinical practice in head and neck cancers, especially when treating skin cancers and superficial neck nodes, and will not be discussed in detail in this chapter. On the other hand, protons and other heavy particles require specialized and more costly machines (e.g., a cyclotron) that have only become commercially available in the last few decades, limiting the experience that exists in treating head and neck cancers. Particles have potential physical properties that can improve conformality of radiation delivery and may increase tumor kill defined as relative biologic effect (RBE).

7.1 Proton Radiotherapy

There is convincing biological and physical evidence to support the use of particle therapy (e.g., protons, neutrons, and heavy ions) in radiation oncology. Proponents of charged particle therapy tout the potential to improve local control while sparing adjacent normal tissue. This is due to the deposition of the maximum amount of energy near the end of an ion track, termed the Bragg peak, which can be used to spare critical excessive radiation dose to nearby organs-at-risk (e.g., for treatment of skull base tumors in close proximity to the optic apparatus or brainstem) (Fig. 8) (Kosaki et al. 2012). Protons or carbon ions stop immediately following this peak of energy deposition limiting the radiation dose to distal structures, in comparison to photons which continue to travel through the body and deposit energy distal to a target. Proton therapy has been used in the treatment of cancer since the 1950s. However, with recent increased interest, and with the help of modern technology, construction of many facilities across the USA has increased the number of patients being treated and the clinical experience treating head and neck cancer is rapidly expanding.

Proton beam RBE is traditionally reported as 1.1, which is about 10% greater biological effectiveness than photon therapy. However, there is experimental data showing proton RBE is

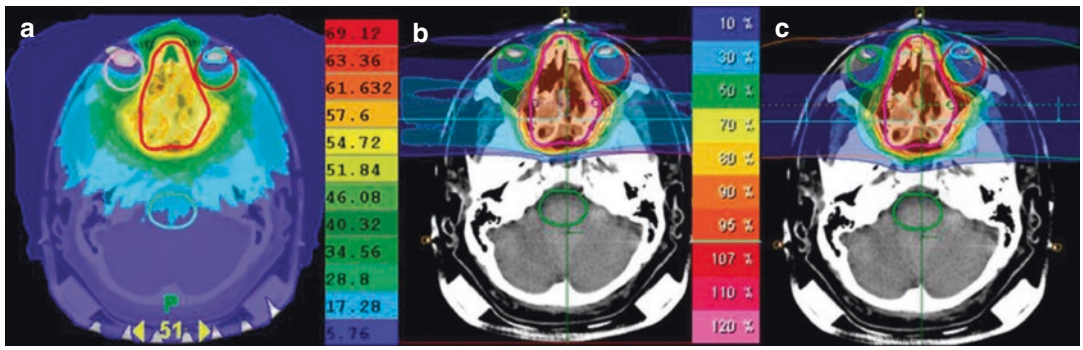


Fig. 8 Dose distributions in transverse plane for (**a**) photon IMRT, (**b**) carbon ion and (**c**) proton treatment planning techniques for a patient with a skull base meningioma. The same beam arrangements were used for carbon ion and proton plans. These plans consisted of two lateral beams and one cranial–caudal beam. Particle radiotherapy (**b**, **c**) spares the brainstem and cochlea from low-dose radiation (light and *dark blue* volumes). Figure courtesy of Kosaki et al. Radiation Oncology 2012;7:44 (Kosaki et al. 2012)

dependent on various factors including dose per fraction, depth of spread out Bragg peak, and the alpha/beta ratio of target tissue (Gerweck and Kozin 1999). Still, this slight advantage in RBE is not the driving force behind the recent interest in proton therapy. Rather, it is the steep dose distribution found with protons, particularly the sharp beam penumbra and lack of exit dose. These physical properties improve therapeutic ratio by lowering dose to normal tissues and allowing dose escalation to tumors.

7.1.1 Skull Base Chordoma/ Chondrosarcoma

One of the first clinical uses of proton therapy was for treatment of chordomas and chondrosarcomas of the base of skull; base of skull location makes these tumors very challenging to resect and they are known to locally recur when a gross total resection is not performed. Multiple single institutional retrospective data have reported local control rates of 54–100% with proton beam radiotherapy (Rombi et al. 2013; Ares et al. 2009; Rutz et al. 2008; Noel et al. 2005; Munzenrider and Liebsch 1999; Pommier et al. 2006); this is a significant improvement compared to historical controls treated with photon external beam radiotherapy with control rates of less than 25% (Catton et al. 1996; Zorlu et al. 2000). The largest of these series, Munzenrider and Liebsch (1999) reported outcomes on 519 patients with skull base chordoma and chondrosarcoma treated with 66–82 cobalt Gray equivalent proton–photon mixed radiation with reports of locoregional failure free survival of 73% at 5 years. However, this dose escalation with proton beam therapy was not without significant toxicity as three patients died of brainstem injury and eight patients had temporal lobe injury, as well as reports of hearing loss, cranial neuropathy, and endocrinopathies (Munzenrider and Liebsch 1999).

7.1.2 Nasal Cavity/Paranasal Sinuses

The typical treatment paradigm for paranasal sinus and nasal cavity cancers includes large surgical resections followed by adjuvant radiation or chemoradiation. Resto et al. (2008) published the largest reported retrospective review of 102 patients with locally advanced sinonasal cancers treated with proton beam or mixed proton–photon beam at Massachusetts General Hospital (MGH) between 1991 and 2002. Five year local control rates were excellent regardless of extent of resection: 95% (complete resection), 82% (partial resection), and 87% (biopsy only) (Resto et al. 2008); compared to single institution reports of external beam photon radiotherapy with control rates of 56–78% at 5 years (Myers et al. 2002; Jansen et al. 2000; Jiang et al. 1991). However, this excellent local control seen with proton beam radiotherapy didn't translate to better disease-free survival as patients with partial resection and biopsy only had a 5-year disease-free survival of 49% and 39%, respectively. Patients undergoing complete resection had an excellent 5-year disease-free survival of 90% (Resto et al. 2008).

7.1.3 Nasopharynx

Very limited data exists regarding the use of proton therapy for nasopharyngeal cancer outside of reports of re-irradiation from Loma Linda (Lin et al. 1999) and Lawrence Berkeley National Laboratory (Feehan et al. 1992). These small series report outcomes on 16 and 11 patients, respectively; with local control rates of 45–50%. Two abstracts from MGH have been presented on proton therapy in nasopharynx cancer, however, neither has yet to be formally published (Chan et al. 2004, 2012). Chan et al. reported the use of proton/photon therapy with chemotherapy to treat 17 patients with T4 nasopharynx carcinoma at the 2004 American Society of Clinical Oncology meeting. Three year locoregional control was 92%. These authors later reported on the use of proton/photon chemoradiation to treat 23 patients with stage III–IVB primary nasopharynx cancer at 2012 American Society for Radiation Oncology (ASTRO). At a median follow-up of 28 months, they reported no local or regional failures. MD Anderson has reported a single institution series of nine patients treated with intensity-modulated proton therapy with 2-year locoregional control of 100% and 2 year overall survival of 88.9%. This report also observed a dosimetric advantage of protons compared to

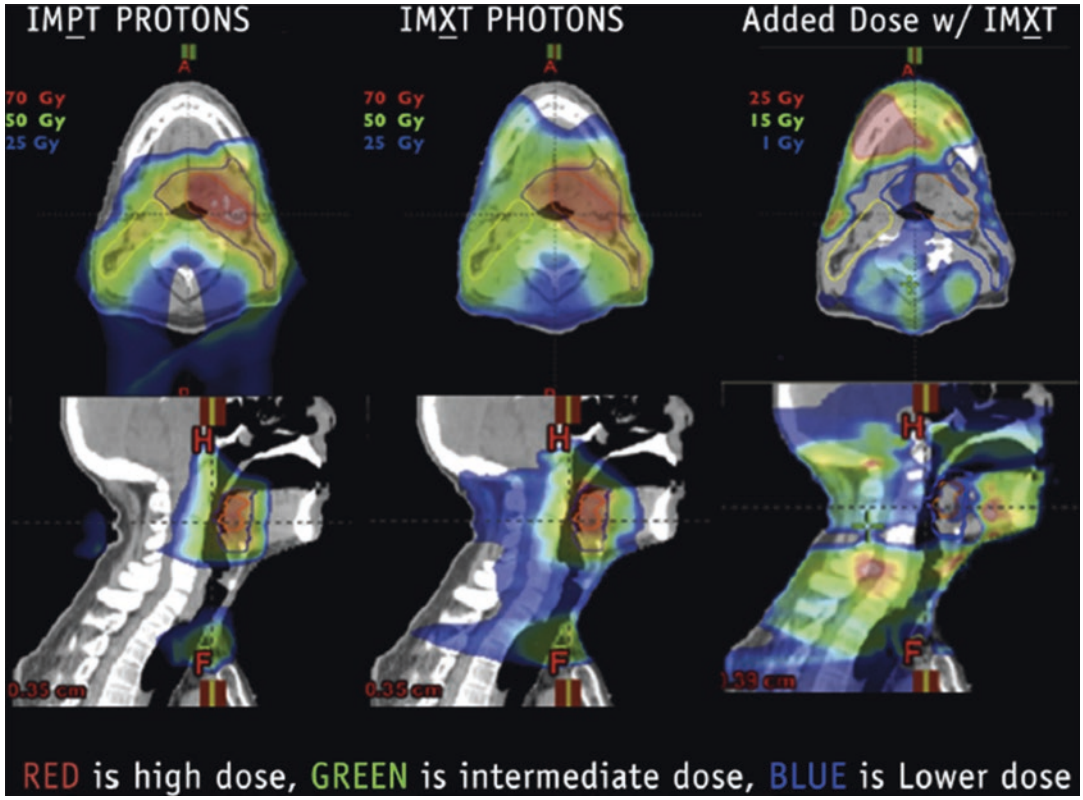


Fig. 9 Oropharyngeal cancer patient with intensity-modulated proton (*left*) and photon (*middle*) plans. The excess from the photon plan is shown in the plan on the *right*. Figure courtesy: Frank IJROBP 2016;95:37–39 (Frank 2016)

IMRT photon plans generated for the same patients (Lewis et al. 2016). However, it is unknown if this translates into clinically meaningful reduced toxicity.

7.1.4 Oropharynx

There is currently no published data outside of re-irradiation with proton therapy in oropharyngeal cancer. The theoretical advantages are in limiting the integral dose to non-target organs at risk; this is represented well in Fig. 9, which shows a visual comparison of an intensity-modulated proton beam therapy (IMPT) and IMRT photon plans in the same oropharyngeal cancer patient (Frank 2016).

MD Anderson Cancer Center is currently enrolling oropharyngeal patients in a phase II/III randomized trial comparing IMPT to IMRT [NCT01893307]. This trial will treat both groups to 70 Gy equivalent in 33 fractions, with the primary endpoint being the development of chronic grade 3 or higher toxicity during the first 2 years after completion of radiation therapy (Frank 2016) [http://clinicaltrials.gov/show/NCT01893307. Accessed May 21, 2016].

7.2 Heavy Ion Radiotherapy

Heavy ion therapy, most commonly carbon ion therapy, uses particles with more mass than neutrons or protons. Heavy ions have the steep dose distribution of protons while having a much higher RBE; which has the potential to have the greatest impact in radioresistant tumors. Carbon ions are generally used as a boost to photon therapy for head and neck cancers and data is limited to a few institutions (Mizoe et al. 2004, 2012; Schulz-Ertner et al. 2003; Kamada et al. 2015; Rieken et al. 2011). A phase I/II trial evaluating

carbon ion radiotherapy in recurrent nasopharyngeal carcinoma is ongoing in Japan to determine optimal dosing and efficacy (Kong et al. 2016). As of June 2016, there are currently no carbon ion centers in the USA.

7.3 Neutron Radiotherapy

Neutrons have high relative biological effectiveness (RBE) that may offer an advantage compared to photon radiotherapy, especially in known radioresistant and hypoxic tumors. This theoretical advantage is from high linear energy transfer (in the range of 200 KeV/μm for 2 MV neutrons) which is about 200-fold that of photons. With an RBE in the range of 2–8, a single Gray of fast neutron therapy has the killing effect of 2–7 Gy of photons (Schmid et al. 2003; Battermann et al. 1981). Neutrons also have a low oxygen enhancement ratio (OER), giving a theoretical advantage over photons in hypoxic tumors. It is these biological and physical advantages which drove fast neutron therapy into the limelight in the 1970s to the mid-1980s. However, neutrons were mostly abandoned in the late 1980s due to unacceptable side effects including soft tissue fibrosis and necrosis. Few randomized trials comparing photons and neutrons exist for cancer therapy. Still, a randomized trial comparing the two was performed in salivary gland tumors (Laramore et al. 1993). This trial was performed by Radiation Therapy Oncology Group (RTOG) in the USA and the Medical Research Council (MRC) in Great Britain and randomized inoperable primary or recurrent salivary gland malignancies to fast neutron radiotherapy versus conventional photon and/or electron radiotherapy. With poor prior results at that time with conventional radiotherapy and the often superficial location of salivary gland malignancies, it was felt to be an ideal tumor model for early neutron studies. The initial RBE calculation of neutron therapy in treating adenoid cystic salivary gland cancer was 8.0, while the RBE of neutrons on normal tissue in those same studies was only 3–3.5 (Battermann et al. 1981). This meant a dose of 20 neutron Gy to a parotid tumor had the biological effect of 60–70 Gy on normal tissue while delivering a biologic effect on the tumor equivalent to 160 Gy, a therapeutic gain of 2.3–2.6. This radiobiologic rational was the basis for the RTOG/MRC trial. Only 32 patients were ultimately enrolled with 25 eligible and evaluable, at four institutions: Fermi Laboratory, Edinburgh, Scotland, University of Pennsylvania, and the University of Washington. Neutron dosing was scaled according to the RBE of the individual facility over 12 fractions in 4 weeks, with the control photon arm receiving 70 Gy over 7.5 weeks. Locoregional control was 67% for the neutron group compared to 17% ($p < 0.005$) for the photon group at 2 years. Two-year overall survival was 62% for the neutron group versus 25% in the photon group ($p = 0.1$) (Koh et al. 1989). This study was closed early given the dramatic differences in locoregional control. Ten-year follow-up shows locoregional control of 56% in the neutron group versus 17% in the photon group, which remains significant. However, the apparent survival benefit seen at 2 years was lost by 10 years: 15% for the neutron patients versus 25% for the photon patients. Study limitations include small sample size and unbalanced treatment arms. Neutrons resulted in a higher incidence of severe morbidity compared to photons (Table 1).

At the peak of neutrons' use, there were eight active centers in the USA. In 2015, due to diminishing demand and closure of all but the University of Washington facility, the NCCN

Table 1 Grade 3 and greater toxicities as reported in RTOG/MRC neutron trial (Laramore et al. 1993)

	Photons	Neutrons
Hoarseness	0	1
Dysphagia	1	2
Dehydration	1	2
Malnutrition	1	2
Pain	0	3
Mucosal	1	3
Skin	2	2
Fibrosis	1	2
Necrosis	0	3
Xerostomia	2	1
Impaired taste	1	4
Other	0	1

guidelines have removed recommendations for neutron therapy for salivary gland cancers from their primary pathway. Neutron therapy is still listed as footnote for selected patients (Pfister et al. 2015). The toxicity concerns, cost, and lack of randomized data (only salivary gland malignancies) have resulted in the diminished use of neutron therapy over time.

With the current lack of data supporting clear indications for the use of proton beam and heavy ion therapy in head and neck cancers, as well as the limited number of patients who have potential access to the few facilities, current NCCN Guidelines limit any specific recommendations for their use in head and neck cancers (Pfister et al. 2015). In the modern, cost-centered healthcare era, although proton beam and heavy ion therapy sport advantageous physical and hypothetical benefits, it is unlikely their use will be adopted until supportive clinical data exists.

Conclusion

Radiotherapy for head and neck cancer continues to improve with advances in technology. Treatment planning techniques and protons have improved our ability to deliver radiotherapy more precisely. With the increase in HPV-associated oropharyngeal cancer, we are facing a new disease entity which is fortunately responsive to radiation and chemotherapy. This radiosensitive disease combined with our improvements in technology has led to questions regarding reduction in radiation dose and volumes. While we seek to reduce the considerable morbidities of our therapy, we hope to improve our control and ultimately our cure of head and neck cancer.

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Pediatric Cancer

Arnold C. Paulino

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Abstract

Current strategies in pediatric oncology have utilized an approach which balances the probability of cure and risk of acute and late toxicity from treatment. This chapter will discuss some of the recent development in pediatric radiation oncology and explores the different strategies that have been utilized, Many of the strategies have decreased either dose or volume of radiotherapy; however, in certain scenarios, the role of radiotherapy has expanded to include treatment of young children < 3 years with brain tumors, treatment of metastatic disease as part of initial therapy and use of reirradiation.

1 Introduction

Pediatric radiation oncology is a constantly changing subspecialty of radiation oncology. Current treatment strategies have evolved to minimize volumes exposed to radiation and doses delivered to

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critical surrounding structures. Because the late toxicity of radiotherapy includes inhibition of normal development and/or function of an organ, children are particularly more vulnerable than adults, with more recognizable somatic effects. In general, there is a trend for the use of less radiotherapy in patients with childhood malignancies, although in specific situations, radiotherapy has more roles such as in infant brain tumors and in the metastatic and relapsed setting. This chapter outlines some of the developments in the past few years in pediatric radiation oncology. These topics include the omission of radiotherapy, the lowering of dose and minimizing volume of surrounding organs irradiated, the use of more advance technology to diminish late effects and use of radiotherapy, and the expanding role of radiotherapy in infants and metastatic/relapsed disease.

2 Omission of Radiotherapy

2.1 Wilms' Tumor and Whole-Lung Irradiation

While it has been standard to deliver postoperative radiotherapy (RT) to the hemiabdomen of patients with Stage III favorable histology Wilms' tumor, the value of whole-lung irradiation in children with lung metastasis has recently been under investigation. While traditionally, chest radiographs have been used to determine presence of pulmonary metastasis, computed tomography (CT) scan of the chest has become the imaging of choice for staging. Smaller nodules can be detected better by CT scan; however, not all nodules are secondary to tumor and may be a result of atelectasis, hamartoma, granuloma, or other infectious process. In addition, there has been interobserver variability among pediatric radiologists on what to call metastatic disease on chest radiograph and computed tomography (Wilimas et al. 1997). The International Society of Pediatric Oncology (SIOP) study showed that the use of actinomycin-D, vincristine, and doxorubicin converted most patients with chest X-ray-positive lung metastasis to chest X-ray negative. For patients with remaining lung nodules that were not resected after initial chemotherapy, 15 Gy whole-lung irradiation was delivered. The 5-year recurrence-free survival with this approach was 83 % with 26 of 36 children being able to avoid whole-lung irradiation (De Kraker et al. 1990). This survival outcome is comparable to the National Wilms Tumor Study group approach of delivering whole-lung irradiation to chest X-ray-positive patients (Green et al. 1998). For children with CT scan-positive, chest X-ray-negative lung metastasis, a retrospective study from St. Jude indicates an increase in pulmonary relapses when WLI was not employed (Wilimas et al. 1988). A review of NWTS-3 and NWTS-4 did not reveal any event-free or overall survival difference in children receiving WLI or not. The UKW2 showed pulmonary relapse in three of seven children with local Stage I, chest CT-positive disease when WLI was not used; however, these patients received vincristine monotherapy (Owens et al. 2002). The importance of chemotherapy is highlighted in a NWTS-4 and NWTS-5 study which showed that the use of doxorubicin in addition to actinomycin-D and vincristine was associated with a better 5-year relapse-free survival (79.7 % vs. 54.4 %, $p = 0.01$) in patients with CT-positive lung nodules only. In the same group of patients, the use of WLI did not improve the 5-year relapse-free survival (Grundy et al. 2012). Recently, the Children's Oncology Group (COG) AREN0533 study treated patients according to the response of pulmonary metastasis to 6 weeks of actinomycin-D, vincristine, and doxorubicin. Patients with favorable histology tumors with no extrapulmonary metastasis and loss of heterozygosity (LOH) at 1p and 16q were eligible for WLI omission if CT of the chest at 6 weeks was negative for pulmonary metastasis. Patients who did not achieve a complete response (CR) received WLI and received more aggressive chemotherapy with the addition of cyclophosphamide and etoposide (Regimen M). Approximately 58 % of the patients did not achieve a CR and received WLI and Regimen M with a 3-year event-free and overall survival of 88 % and 92 %, better than historical control of patients with lung metastasis in previous NWTS trials (Dix et al. 2014). The survival outcomes of patients who had a CR to chemotherapy and did not receive WLI are still pending.

2.2 Hodgkin Lymphoma and Involved Site Radiotherapy

With long-term survival rates more than 90 %, patients with Hodgkin lymphoma are currently being treated using a response-based approach with the goal of reducing or eliminating radiation therapy (RT) in the treatment schema. Secondary malignancies and cardiovascular, pulmonary, and thyroid late effects have been documented in long-term survivors of Hodgkin lymphoma. Initial reports of the Children's Cancer Group (CCG) trial C5942 showed a significantly lower 10-year event-free survival but the same overall survival in patients treated with cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (COPP/ABV) hybrid chemotherapy alone compared to those receiving both COPP/ABV and involved-field radiotherapy (IFRT). It was felt that the chemotherapy used in this study was less intensive compared to contemporary trials (Nachman et al. 2002). In the German Pediatric Oncology Group (GPOH) trial HD95, RT was not given in patients receiving an anatomic CR after vincristine, etoposide, prednisone, and doxorubicin (OEPA)-COPP chemotherapy. The 10-year progression-free survivals were lower in intermediate and high-risk patients who had a CR compared to those who did not achieve a CR and received IFRT (Dorffel et al. 2013). It was felt that assessment by anatomic response at completion of chemotherapy might not be adequate to identify which patients can avoid IFRT without increasing risk of relapse. In more contemporary trials using more intensive chemotherapy and functional imaging to assess response, a subset of patients has been identified who can avoid IFRT. The Children's Oncology Group (COG) trial AHOD0031 for intermediate-risk Hodgkin lymphoma eliminated IFRT if after two cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) chemotherapy, an anatomic response of more than 80 % and a negative gallium 67 or FDG-PET scan at the end of chemotherapy were achieved without compromise of event-free and overall survival (Friedman et al. 2014). In the COG AHOD0431 trial for low-risk Hodgkin lymphoma, preliminary results indicate that the omission of IFRT does not compromise event-free or overall survival in patients with a negative PET scan after one cycle of doxorubicin, bleomycin, vincristine, and cyclophosphamide (ABVC) chemotherapy (Castellino et al. 2014).

2.3 Intracranial Germinoma and Chemotherapy Alone

Intracranial germinomas are both radiosensitive and chemosensitive. More than 90 % of patients with intracranial germinoma can be cured by RT alone. Traditionally, these patients have been treated with craniospinal irradiation, and there has been some concern among pediatric oncologists regarding the associated cognitive, endocrine, and carcinogenic effects of RT. Several studies have attempted to eliminate RT by using multiagent chemotherapy. The First International CNS Germ Cell Tumor Study delivered four cycles of carboplatin, etoposide, and bleomycin; those with a CR had two more cycles, while those who did not achieve a CR received two cycles with the addition of cyclophosphamide. Overall, 37 of 45 (82 %) patients with germinoma had a complete response to chemotherapy; however, approximately half of the patients either relapsed or progressed with nearly all being salvaged by the use of RT (Balmaceda et al. 1996; Merchant et al. 1998). Two other international studies have used either intensive cisplatin and cyclophosphamide or carboplatin/etoposide alternating with cyclophosphamide/etoposide or carboplatin, cyclophosphamide, and etoposide. While these chemotherapy regimens have resulted in most patients achieving a remission, nearly half of the patients fail with a chemotherapy-alone approach (Kellie et al. 2004; Da Silva et al. 2010). The standard treatment for intracranial germinoma remains RT alone or neoadjuvant chemotherapy followed by RT.

3 Reduction of Radiotherapy Volume

3.1 Medulloblastoma: Posterior Fossa Versus Tumor Bed Boost

The standard RT boost field in medulloblastoma has been to include the entire posterior fossa. Recent advances in the radiologic sciences have led to better imaging of tumors and more sophisticated radiotherapy delivery. As a result, several investigators have treated the tumor bed with margin instead of the entire posterior fossa for the boost target. Treating only the tumor bed has advantages over treating the entire posterior fossa, with less dose to the normal brain and cochlea. Several studies have shown that isolated non-tumor bed posterior fossa failures are uncommon and found in <5 % of cases (Wolden et al. 2003; Douglas et al. 2004; Paulino et al. 2011). A recent study from Toronto found that the use of a tumor bed boost instead of a posterior fossa boost was associated with a better neurocognitive outcome (Moxon-Emre et al. 2014). The recently closed COG ACNS 0031 protocol which randomized standard-risk patients to posterior fossa vs. tumor bed boost (tumor bed with 1.5 cm margin for clinical target volume) should help answer the question of the appropriate boost field for medulloblastoma.

3.2 Intracranial Germinoma: Whole Ventricular Versus Involved Site Irradiation

Craniospinal irradiation (CSI) was the standard RT volume that needed to be treated for intracranial germinoma. In the past decade, some investigators have reported that intracranial germinomas can be treated using a whole ventricular field followed by a tumor boost (Rogers et al. 2005). Some investigators have used neoadjuvant chemotherapy followed by RT to the tumor/tumor bed. Unfortunately, relapses in the ventricles were more frequent in patients receiving local field RT even in the setting of chemotherapy, and hence whole ventricular irradiation has become the minimum RT volume that needs to be treated for localized intracranial germinoma (Alapetite et al. 2010). For patients with disseminated germinoma, CSI remains the standard treatment.

4 Reduction of Radiotherapy Dose

4.1 Medulloblastoma: 18 Gy Versus 23.4 Gy for Standard-Risk Disease

Studies which have examined the use of 23.4 Gy for CSI have shown continued cognitive decline; hence, clinicians have investigated dose reduction to 18 Gy for CSI. At the Children's Hospital of Philadelphia and University of Pennsylvania, a prospective trial of 18 Gy CSI and posterior fossa boost to a total dose of 55.8 Gy and chemotherapy in ten children showed a 4-year actuarial survival of 69 % with no marked change in intelligence quotient scores in the survivors (Goldwein et al. 1996). At Indiana University, seven patients, ages 20–64 months, were treated with 18 Gy CSI and 54Gy posterior fossa boost. All patients received 4 months of chemotherapy prior to CSI. Three patients relapsed, all outside the posterior fossa, and two were salvaged. Four of the six survivors had endocrine deficit, and all need special assistance in school (Jakacki et al. 2004). The question of 18 Gy vs. 23.4 Gy in standard-risk medulloblastoma was studied in the COG ACNS 0031 protocol. Children ≤7 years were randomized to one of the two radiotherapy doses; the results of the trial have not been released. Current studies are underway looking at further dose reduction (15 Gy CSI or no CSI) in children with the favorable WNT pathway medulloblastoma which traditionally has been associated with a >90 % survival using CSI followed by boost and chemotherapy.

4.2 Rhabdomyosarcoma: Reduction of Dose for Group III Orbital Tumors

Children with Group III rhabdomyosarcoma have traditionally received 50.4 Gy to areas of

gross disease. Because of the favorable outcome of children with orbital rhabdomyosarcoma, the COG D9602 trial looked at a dose reduction for orbital rhabdomyosarcoma to 45 Gy. Local failure rate was 14 % and was quite similar to the local failure rate of 16 % with 50.4 Gy in the Intergroup Rhabdomyosarcoma Study (IRS)-III (Breneman et al. 2011). In both studies, vincristine and actinomycin-D (VA) were the only chemotherapy drugs given. A look at IRS-IV shows a local failure rate of only 4 % for orbital tumors when three chemotherapy drugs such as vincristine, actinomycin-D, and cyclophosphamide (VAC); vincristine, ifosfamide, and etoposide (VIE); or vincristine, actinomycin-D, and etoposide (VAE) are given (Crist et al. 2001). The subsequent study COG ARST 0331 continued to use 45 Gy with VAC chemotherapy.

4.3 Rhabdomyosarcoma: Reduction of Dose for Group II Tumors with Positive Margins

Retrospective analysis of data from the Memorial Sloan Kettering Cancer Center showed that doses of 30 to 36 Gy may be adequate for resected rhabdomyosarcoma with positive margins (Mandell et al. 1990). In the IRS-IV, patients with resected tumors and positive margin received 41.4 Gy to the primary site. In the COG D9602 study, a dose of 36 Gy with VA chemotherapy was used for favorable sites, resulting in a local failure rate of 15 %. On the other hand, a dose of 36 Gy with VAC chemotherapy was used for unfavorable sites, resulting in a local failure rate of 0 % (Breneman et al. 2011). Again when comparing the D9602 to IRS-III where favorable sites got VA chemotherapy and 41.4 Gy, the local failure rate was also high at 11 %. In IRS-IV where VAC, VIE, or vincristine, actinomycin-D, and ifosfamide (VAI) were used with 41.4 Gy, the local failure rate was only 2 %. For unfavorable sites, IRS-III patients received VA chemotherapy and 41.4 Gy with a local failure rate of 14 %, while IRS-IV patients received VAC, VAI, or VAE chemotherapy and 41.4 Gy with a local failure rate of 7 %. The above results suggest that lowering the dose to 36 Gy for patients with microscopic margin of resection is acceptable when a three-drug chemotherapy regimen is employed.

4.4 Non-rhabdomyosarcoma Soft Tissue Sarcoma and Reduction of Radiotherapy Dose in Group II Tumors with Positive Margins

In adult patients, radiotherapy doses of approximately 66 Gy have been used for non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) with positive margin of resection. In the only prospective study of pediatric patients with resected NRSTS, an age-dependent radiotherapy dosing scheme was utilized. Children with microscopic residual disease received 45 Gy (<6 years) or 50 Gy (≥6 years). Patients with gross residual disease that were judged to be potentially resectable received a preoperative RT dose of 55 Gy (<6 years) or 65 Gy (≥6 years). Local control was achieved in 60 % (9/15) of patients receiving <50 Gy, 81 % (13/16) of patients receiving 50–54.9 Gy, and 94 % (17/18) of patients receiving >55 Gy (Pratt et al. 1999). Retrospective data from St. Jude Children's Research Hospital also imply that a dose >55 Gy may be adequate (Spunt et al. 1999). The COG ARST 0332 examined the use of 55.8 Gy RT to patients with microscopic margins of resection. A preliminary report showed that the 3-year event-free and overall survival rates were 68 and 81 % with ifosfamide and doxorubicin chemotherapy and 55.8 Gy RT which were similar to or better than previous reports using higher doses of RT (Spunt et al. 2014).

5 Use of More Sophisticated Technology

5.1 Use of Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is an RT technological innovation which has been used in the past 20 years. The main advantage of IMRT is to reduce the high dose volume of RT by

being more conformal to the target volume. The major disadvantage is the low-dose radiation in surrounding structures which may not have been delivered with a two-dimensional RT technique. Most clinicians think that the expense of having excess lower dose RT is justified as most complications are caused by high RT. There is a theoretical concern that IMRT may be associated with more secondary carcinomas and leukemias (Hall and Wuu 2003). To date, these concerns have not been supported by clinical data; however, follow-up is short for secondary cancers (Casey et al. 2014). Multiple retrospective series have shown that IMRT gives equivalent local control to pediatric patients treated with 2-D or 3-D techniques. These reports have been described in children with brain tumors and sarcomas (Paulino et al. 2011, 2013a; Curtis et al. 2009; Schroeder et al. 2008; Greenfield et al. 2015; Yang et al. 2012). To date, data regarding improvement in late toxicity has been scarce but has been shown in medulloblastoma children receiving cochlear-sparing IMRT and cisplatin chemotherapy (Paulino et al. 2010).

5.2 Use of Proton Therapy

In the past 10 years, proton therapy has been gaining popularity in the radiotherapeutic management of pediatric tumors. The lack of an exit dose is particularly attractive in children as less dose to normal, surrounding structures should theoretically be better for growing and developing organs. The best use of proton therapy in the author's opinion is in the setting of CSI where doses to the heart, lungs, abdominal organs, and gonads can be minimized or annihilated. There is also a theoretical advantage that protons may reduce secondary cancer risk by elimination of the lower doses of radiation to non-target tissues (Miralbell et al. 2002; Zhang et al. 2014). To date, results of treatment with proton therapy have been equivalent to 3-D and IMRT techniques (Macdonald et al. 2013; Bishop et al. 2014; Ladra et al. 2014). A study from Boston showed that in children with retinoblastoma, the 10-year incidence of secondary malignancy in the RT field was 0% with protons and 14% for photons, while the incidence for all secondary malignancies was 5% with protons and 14% for photons (Sethi et al. 2014). Future studies are underway looking at improvement in late toxicity with the use of proton therapy but follow-up has been short.

6 Expanding Role of Radiotherapy in Pediatric Oncology

6.1 Radiotherapy and Infant Brain Tumors

Twenty years ago, children <3 years of age with brain tumors were treated with a maximal safe resection followed by adjuvant chemotherapy. RT was delayed until the child turned 3 years of age or at the time of relapse. The landmark Baby Pediatric Oncology Group (POG) study showed that chemotherapy can delay the institution of RT; however, the 2-year progression-free survival was only 40% (Duffner et al. 1993). Because of improvement in imaging and RT delivery, some investigators have utilized RT for children <3 years of age. At St. Jude Children's Research Hospital, Merchant and colleagues treated 153 children with localized ependymoma. The median age at time of conformal RT was 2.9 years; the RT dose was 59.4 Gy (≥18 months old) in 131 and 54 Gy (12–17 months old) in 22 patients. The 7-year local control, event-free survival, and overall survival rates were 87.3, 69.1, and 81.0% (Merchant et al. 2009). This compares favorably to ependymoma patients in the Baby POG study with a 1- and 2-year progression-free survival of 58 and 42% and in the French Society of Pediatric Oncology (SFOP) study with a 4-year progression-free survival of 22% (Duffner et al. 1993; Grill et al. 2001). The COG ACNS0121 protocol investigated the use of conformal radiotherapy in pediatric patients; preliminary data showed that the outcome of immediate postoperative RT for children as young as 1 year old was favorable, with about two-thirds of patients being event-free at 5 years (Merchant et al. 2015).

For children <3 years of age with medulloblastoma, the use of CSI has largely been abandoned because of severe neurotoxicity and

Table 1 Outcomes of studies using conventional fractionation reirradiation in pediatric tumors

First author (reference)	Type of tumor (number of patients)	Previous radiotherapy treatment	Reirradiation details	Results
Merchant et al. (2008)	Ependymoma ($N=13$)	40–69.6 Gy local RT	50.4–54 Gy local RT	Three patients developed metastatic disease. The 5-year overall survival was 67 %
	Ependymoma ($N=19$)	37.8–59.4 Gy local RT	35.2–41.4 Gy craniospinal RT, 48.6–59.4 Gy local RT	Of 12 patients with metastatic failure and treated with reirradiation using CSI, 9 did not progress
Bouffet et al. (2012)	Ependymoma ($N=47$)	Various	18 of 47 patients had 54 Gy focal and/or craniospinal RT	3-year overall survival was 7 and 81 % for nonirradiated and reirradiated patients. Two had endocrine dysfunction and one required special education support
Messahel et al. (2009)	Ependymoma ($n=108$ of which 62 had reirradiation))	Various	Various	Surgery and reirradiation at relapse were independent predictors of survival
Eaton et al. (2015)	Ependymoma ($n=20$)	55.8 CGE local RT	Median dose: 50.4 CGE	3-year overall and progression-free survival were 78.6 and 28.1 %
Bakst et al. (2011)	Medulloblastoma ($n=13$)	Various	Various	5-year progression-free and overall survivals were 48 and 65 %. One case of asymptomatic in-field radiation necrosis
Wetmore et al. (2014)	Medulloblastoma ($n=38$ of which 14 had reirradiation)	23.4–39.6 Gy CSI followed by a tumor bed boost to total dose of 55.8 Gy	CSI in 8, spinal in 3, and primary site in 3	5- and 10-year survival rates were 55 and 46 % for reirradiated patients and 33 and 0 % for non-reirradiated patients
Fontanilla et al. (2012)	Diffuse intrinsic pontine glioma ($n=6$)	54–55.8 Gy local RT	2–20 Gy	Four patients had improvement in symptoms. No grade 3 or 4 toxicity

growth abnormalities. For localized desmoplastic medulloblastoma, the prognosis is good with surgery and intraventricular methotrexate-based chemotherapy, without RT (Rutkowski et al. 2005). For localized classic medulloblastoma, prognosis is not as good. Recent data for medulloblastoma M0 children <3 years indicate that the most common pattern of failure is at the primary site (Van Bueren et al. 2011). There has been renewed interest in giving RT, with primary site RT instead of CSI, after surgery and some chemotherapy. The POG 9934 trial incorporated primary site RT as part of the treatment regimen and was associated with less local failure; however, the event-free survival was not statistically different to previous trials which did not receive primary site RT (Ashley et al. 2012).

6.2 Radiotherapy and Dose Intensification in Subtotally Resected High-Risk Neuroblastoma

Primary site irradiation, regardless of extent of surgery, has been advocated in children with high-risk neuroblastoma. Based on information gathered from CCG 3891, there seems to be a dose response for high-risk neuroblastoma at a threshold of 20 Gy (Haas-Kogan et al. 2003). Several

institutions have reported less favorable local control outcomes in subtotally resected tumors with this dose, while others have not (Gillis et al. 2007; Kushner et al. 2001). In the NB97 trial, children with subtotally resected who received 36 Gy had a 3-year event-free survival of 85 % compared to those who did not received RT and had a 3-year event-free survival of 25 % (Simon et al. 2006). Dose escalation is currently being investigated in COG ANBL12P1 protocol where the presurgical tumor bed receives 21.6 Gy, while the residual tumor is given a boost of 14.4 Gy to deliver a total dose of 36 Gy to gross residual tumor.

In addition to primary site irradiation, sites of metastatic disease in high-risk neuroblastoma are also irradiated if they are still metaiodobenzylguanidine (MIBG) avid after induction chemotherapy. A recent publication indicates that this strategy is reasonable provided that there are ≤2 MIBG avid sites after chemotherapy (Mazloom et al. 2014).

6.3 Radiotherapy and Reirradiation

Because of innovations in the radiologic sciences and the fact that many children are living longer from their cancer, reirradiation has become a more common situation encountered in pediatric radiation oncology. Reirradiation can be delivered in the form of hypofractionated or conventional fractionation RT. In brain tumors, radiosurgery has been used for recurrent tumors. Several studies have been published in the literature using conventional fractionated reirradiation, some of which have shown improvement in survival or symptomatology (Merchant et al. 2008; Bouffet et al. 2012; Messahel et al. 2009; Eaton et al. 2015; Bakst et al. 2011; Wetmore et al. 2014; Fontanilla et al. 2012). Table 1 summarizes some of these studies in children with ependymoma, medulloblastoma, and diffuse intrinsic pontine glioma. When compared to those who did not receive reirradiation at relapse, patients who were treated with reirradiation had improvement in overall survival as reported in the Toronto ependymoma and St. Jude medulloblastoma relapsed studies (Bouffet et al. 2012; Wetmore et al. 2014).

6.4 Radiotherapy and Metastatic Bone Sarcomas

Aggressive local therapy with RT and/or surgery to metastatic sites has been shown to be part of the treatment regimen for survivors of metastatic Ewing sarcoma (Paulino et al. 2013b). Recently, stereotactic ablative body radiotherapy (SABR) has been used to treat metastatic bone metastasis in children with nasopharyngeal carcinoma and bone sarcomas. Because the target is very limited, a high dose of radiation can be used to ablate tumor, similar to radiosurgery in the brain. Several adult studies targeting spinal bone metastasis have reported excellent local control with this method of RT delivery (Guckenberger et al. 2014; Sahgal et al. 2009). The current COG AEWS1221 is currently studying the use of SABR in the treatment of metastatic bone disease.

Conclusions

While it is not possible to include all the recent developments in pediatric radiation oncology, the above constitute some of the more common diseases and scenarios the radiation oncologist will see in the clinic. The other recent development that was alluded to in this chapter is the characterization by molecular subtype of many pediatric tumors. This is particularly important in the current treatment of medulloblastoma where the WNT pathway tumors are getting less intensive treatment, while other subtypes may be getting more intensive treatment. The future of pediatric radiation oncology is exciting with molecular stratification and development of innovative radiologic technologies.

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Benign Primary Brain Tumors

Samuel E. Day and Lia M. Halasz

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Abstract

Radiation therapy plays an integral role in the management of benign primary brain tumors as either primary or adjuvant treatment. These tumors are generally associated with good prognosis, which makes consideration of the risk of late treatment toxicity especially important. Though they are nonmalignant, benign primary brain tumors can certainly cause significant morbidity or even mortality owing to their intracranial and skull base locations, with possible mass effects on the cranial nerves or the brain itself. Given the competing considerations of toxicity and therapeutic need, controversy frequently surrounds the decision between the use of surgery and radiation therapy for primary treatment. When surgery is limited or resection is subtotal, there may also be controversy regarding the timing of. In radiation therapy addition, as technological advancements in planning and delivery of conformal radiation therapy allow for decreased risk of acute and long-term side effects, additional controversies over fractionation (e.g., standard fractionation versus radiosurgery) and the technique for delivery of radiation therapy (e.g., protons versus IMRT) are ongoing. In this chapter we highlight the controversies in management of meningioma, vestibular schwannoma, craniopharyngioma, pituitary adenoma, and glomus tumor and review the pertinent literature.

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1 Meningioma

Meningiomas are the most common class of primary brain tumor, representing approximately 30% of all primary intracranial neoplasms (Whittle et al. 2004). The term refers to a group of tumors arising from the meningeal coverings of the central nervous system. The likelihood of development of meningioma is proportional to patient age, with most diagnoses being made during the sixth to seventh decade of life (Wiemels et al. 2010). The prevalence of pathologically confirmed meningioma is estimated to be approximately 97.5/100,000 in the United States; however, there has been an increase in the number of radiographically detected, clinically occult lesions being described in the era of modern medical imaging (Vernooij et al. 2007).

Although 75% of meningiomas are WHO grade I lesions that progress slowly and are considered benign, meningioma cell types are nonuniform, and growth rates and growth patterns may vary dramatically between different patients (Louis et al. 2007). Meningiomas may exhibit varying degrees of anaplastic features, with aggressive growth patterns leading to significant morbidity due to local infiltration, mass effect, and a propensity for recurrence after surgical resection (Mahmood et al. 1993; Jääskeläinen et al. 1986; Perry et al. 1999, 1997). In addition, even indolent tumors can cause significant morbidity from local growth, associated edema, or transformation to higher grade lesions, ultimately necessitating treatment despite their favorable biology.

WHO grade II meningiomas are characterized by hypercellularity, frequent mitoses, sheeting architecture, and increased growth rates. They represent ~20% of lesions, with a recent increased incidence following revised WHO grading criteria published in 2007 (Louis et al. 2007). Ultimately, WHO grade represents an important prognostic factor; when compared to WHO grade I meningioma, atypical tumors have a seven- to eightfold risk of recurrence at 3–5 years. Finally, roughly 5% of meningiomas are WHO grade III anaplastic tumors, characterized by significant cellular dedifferentiation, malignant potential, and aggressive growth (Louis et al. 2007), with correspondingly poor outcomes and high risk of progression and spread. These tumors typically have high mitotic indices, increased nuclear-cytoplasmic ratio, and morphologic appearance resembling sarcoma, carcinoma, or melanoma phenotypes.

The variability of the natural course of the disease complicates the study of outcomes, as diverse patients may be lumped together in cohort studies. Due to the generally slow nature of their growth, establishment of validated treatment paradigms in many cases proves difficult owing to a lack of long-term data. Consequently, there remain a number of controversies about the optimal management of patients with meningioma.

1.1 Imaging-Defined Meningioma

Meningioma has a typical and characteristic imaging appearance, described by sharply circumscribed, homogeneous, extra-axial mass lesions with broad involvement of the dura. Following application of intravenous contrast, these tumors exhibit a strong pattern of fairly homogeneous contrast enhancement. Sometimes nearby bone has hyperostosis or osteolytic changes (O'Leary et al. 2007). Such characteristic imaging findings may obviate the need for histopathologic diagnosis in many cases, and incidental detection and diagnosis of imaging-defined meningiomas is increasing in the modern era due to the proliferation of medical imaging.

As the majority of meningiomas are slow-growing benign lesions, active surveillance alone may be appropriate in otherwise asymptomatic patients. Watchful waiting can be pursued until it is obviated by sustained growth, symptomatic presentation, or involvement of critical structures. However, many questions and controversies remain regarding the natural course of incidentally detected imaging-defined lesions and when observation alone versus active management may be preferable; stratification factors identifying patients at greatest risk for tumor growth or symptomatic presentation are poorly defined in the absence of pathological information. It is clear that many of these patients will

eventually require treatment (Yoneoka et al. 2000; Olivero et al. 1995; Nakamura et al. 2003). In one large series of observed tumors over approximately 4 years, 74% of tumors grew according to volumetric criteria, with roughly one third of those requiring treatment during that time (Oya et al. 2011). However, more longitudinal studies into long-term patient outcomes after simple observation are needed.

When possible, surgical resection generally remains the mainstay of definitive therapy. The Simpson grading scale has been utilized historically to describe the extent of resection of a meningioma, any dural attachments or extradural extension. The Simpson resection depends on intraoperative observations and ranges from 1 to 5, where Simpson 1 corresponds to complete removal of all tumor, associated dural attachments, and involved bone, while Simpson 5 is simple decompression only. In most studies, a Simpson grade 1–3 resection typically is considered a GTR (Gallagher et al. 2016; Simpson 1957), with the difference between various Simpson grades of GTR being largely dependent upon intraoperative observations. Ultimately, successfully achieving GTR remains an important prognostic factor in patients with all grades of meningioma (Gallagher et al. 2016), with subtotal resection resulting in increased risk of recurrence (Mirimanoff et al. 1985; Black 1993). Unfortunately, in approximately 30% of cases, GTR is impossible owing to tumor location or proximity to eloquent structures (Mirimanoff et al. 1985); this is especially true in meningiomas involving the base of skull, where up to 50% of tumors are incompletely resectable (Levine et al. 1999; Mathiesen et al. 1996). Even following successful GTR, there remains a significant subset of patients whose disease is poorly controlled with surgery alone, suggesting that aggressive surgical management is not a panacea in meningioma management.

Though surgery has long been the mainstay of treatment of image-defined meningioma, primary radiation therapy has emerged as a viable alternative. Historically, radiation therapy without surgery was used when surgical morbidity would be high due to tumor location or extent. For example, there is a considerable body of literature regarding primary radiation therapy in the setting of optic nerve sheath meningioma owing to the high rates of blindness associated with optic nerve infarction during surgery for this condition (Turbin et al. 2002; Andrews et al. 2002). Published data suggests that these tumors regress or remain stable in greater than 90% of cases after primary radiation therapy alone (Andrews et al. 2002; Becker et al. 2002; Milker-Zabel et al. 2009; Arvold et al. 2009).The success of treatment of meningioma in this setting has contributed to the interest in treating meningiomas of other locations with primary radiation therapy.

For surgically accessible tumors, controversy remains regarding primary radiation therapy given concern about treating meningioma without determining the histology. However, success in the use of stereotactic radiosurgery (SRS) to treat imaging-defined meningioma suggests there may be a viable strategy of minimally invasive radiation therapy in patients with imaging-detected meningioma regardless of histology. One institutional study of 41 patients treated definitively with radiation therapy based on imaging alone described an 8-year actuarial control rate of 94%, with tumors well controlled in 39 of 41 patients, and only minimal complications (Korah et al. 2010). Another published retrospective observational analysis of more than 4500 patients with a median follow-up of 63 months included approximately 3000 imaging-defined meningiomas treated with radiosurgery alone. Overall, tumor control, defined as a reduction in volume or stable size, was 92.5% in this study (Santacroce et al. 2012). Given the slow growth of these tumors and the possibility of late recurrence, longer term follow-up is warranted, but the evidence supporting the use of primary radiation therapy in imaging-defined meningioma is accumulating.

Given these superior outcomes after treatment for imaging-defined meningioma, there is also concern that postoperative changes make it difficult to clearly define and target residual tumor with high-dose, conformal techniques. Santacroce et al. noted that previous surgery was associated with poorer outcomes when treating meningioma and surmised that this may be due to altered

tumor morphology and development of scar tissues complicating target delineation after surgery (Santacroce et al. 2012). Alternatively, this may have been due to selection bias as those who require radiosurgery after surgical resection represent a patient population with more aggressive tumors.

1.2 WHO Grade I Meningioma After Subtotal Resection

A number of series have evaluated the role of SRS or external beam radiation therapy (EBRT) in the adjuvant setting following subtotal resection of atypical or anaplastic meningioma, or after recurrence of lower grade lesions. Adjuvant radiation therapy has improved outcomes in patients with subtotal resection of higher grade lesions or in cases of tumor recurrence following initial surgery. Radiation therapy is clearly indicated for atypical or anaplastic meningiomas after subtotal resection (Wen et al. 2010; Alexiou et al. 2010; Aizer et al. 2014; Lee et al. 2013; Hammouche et al. 2014; Mair et al. 2011; Sun et al. 2014), but controversy remains regarding the role of radiation therapy following subtotal resection of a grade 1 meningioma. For many patients, a close observation of the residual lesion is all that is needed. Considering the long lifespan of patients diagnosed with WHO grade 1 meningioma, long-term studies are required to establish the risks of recurrence or death.

Numerous studies have looked into the rates of recurrence of benign meningiomas following STR alone, with findings of 5-year recurrence rates ranging from 37 to 62% and 10-year local progression of 52–100% (Mirimanoff et al. 1985; Soyuer et al. 2004; Wara et al. 1975; Barbaro et al. 1987; Condra et al. 1997; Miralbell et al. 1992; Stafford et al. 1998). In one of these papers, Condra et al. noted that STR significantly affected cause-specific survival (CSS) in patients with benign meningioma. They reported that 15-year CSS dropped from 88 to 51% when comparing GTR to STR in patients with resected grade 1 meningioma. Furthermore, they noted that the addition of radiation therapy increased CSS at 15 years to 86% in patients with STR of benign meningioma. Unfortunately, these studies were conducted in an era prior to the recent WHO staging revisions and are therefore convoluted by the fact that they also include what would now be classified as grade 2 and 3 patients. In a modern analysis that utilized WHO 2007 classifications, subtotal resection of 236 grade 1 lesions was found to be a factor in reduced progression-free survival and overall survival (Jensen and Lee 2012), lending support to the idea that even in patients with benign meningioma, adjuvant radiation therapy may be warranted. Additional studies into adjuvant therapy after STR are needed to guide practice.

1.3 WHO Grade II Meningioma After Gross Total Resection

There remains controversy regarding the role of radiation therapy following surgical resection of grade II, atypical meningiomas. There is general agreement that GTR alone of atypical meningioma runs the risk of recurrence, and historically these recurrences have been addressed using a strategy of serial re-resection, with some small single-institution studies suggesting only minimal benefit to addition of adjuvant radiation therapy (Goyal et al. 2000). Adjuvant radiation therapy has been commonly used in the setting of STR of atypical meningioma, and multiple studies have been published detailing experiences with stereotactic radiosurgery (SRS) (Kano et al. 2007; Attia et al. 2012; Skeie et al. 2010) or external beam radiation therapy (EBRT) for these patients (Condra et al. 1997; Boskos et al. 2009; Aghi et al. 2009; Milosevic et al. 1996; Hug et al. 2000; Coke et al. 1998).

What is clear is that even optimal surgery is often insufficient in this patient group. In one study that utilized institutional criteria for the grading of meningioma, 45 patients with atypical tumors underwent surgery, achieving GTR. In this cohort the median time to recurrence was 2.4 years, with a 5-year local recurrence rate of 38% (Jääskeläinen 1986). A second study, also utilizing institutional grading parameters, detailed the outcomes of 47 patients with atypical meningioma treated with surgery. In this group, 5-year local recurrence risk was found to be 38%,

increasing to 46% at 15 years. Cause-specific survival reported at 15 years was 57% (Condra et al. 1997). A third single-institution retrospective series of 45 patients with a diagnosis of atypical meningioma showed a strong trend toward lower rates of recurrence of atypical meningioma after GTR followed by radiation therapy when compared to GTR alone; unfortunately this study was hampered by low power and small numbers (Komotar et al. 2012).

More recent studies using validated WHO grading criteria of atypical meningioma show similarly poor outcomes following GTR alone. In one review of 108 patients who underwent Simpson grade 1 GTR of atypical meningioma, the 5-year local recurrence rate was 41%. In this study, disease-specific survival after first recurrence was 86% at 5 years and 69% at 10 years (Aghi et al. 2009), suggesting the patients are at increased risk for death from their disease even after complete surgical excision. Despite this, the largest study of postoperative radiation therapy in patients with grade 2 meningioma found no clear benefit of postoperative XRT after GTR, although a minority of patients received adjuvant radiation therapy so selection bias may have contributed to these results (Mair et al. 2011). In addition, the median dose delivered was 51 Gy, which is lower than subsequent series suggesting the improvement in outcomes with adjuvant radiation therapy.

Given the high risk of local recurrence even after GTR of atypical meningioma, a number of clinicians and investigators have recommended early postoperative radiation regardless of the extent of resection (Aghi et al. 2009; Hug et al. 2000; Park et al. 2013), while others advocate for observation alone with radiation being reserved for salvage at the time of recurrence (Goyal et al. 2000; Pearson et al. 2008). The ROAM/EORTC-1308 trial is addressing this question by randomizing patients to radiation therapy (60 Gy in 30 fractions) versus active monitoring after resection. Outcomes include PFS as well as OS, quality of life, and neurocognition (Jenkinson et al. 2015) and will hopefully guide future clinicians determining those situations where adjuvant radiation therapy after gross total resection of atypical meningioma is warranted. In addition two prospective phase II clinical trials (RTOG-0539 and EORTC 22042–26042) examining the effects of radiation therapy for patients with gross totally and subtotally resected atypical meningiomas have recently finished accrual.

1.4 Dose Selection for WHO Grade II and III Meningioma

Though doses of 50–55 Gy in standard fractionation have led to excellent local control rates for benign meningioma, the optimal dose for the treatment of atypical and malignant meningioma remains unclear. Higher radiation therapy doses do appear to improve local tumor control for these patients. In an early study, Milosevic and colleagues found a 5-year cause-specific survival of 42% with at least 50 Gy versus 0% with less than 50 Gy for patients with grade II and III meningioma after either STR or GTR (Milosevic et al. 1996). For patients with malignant meningioma, Goldsmith and colleagues reported a 5-year PFS rate of 63% using greater than 53 Gy versus 17% with no more than 53 Gy (Goldsmith et al. 1994). Subsequently, dose escalation reports utilizing approximately 60 Gy were published with better results for patients with atypical meningioma. After a median follow-up of 3.2 years, Aghi and colleagues observed no local recurrences with 59.4–61.2 Gy in eight patients who received postoperative radiation therapy for atypical meningioma (Aghi et al. 2009). Similarly, Komotar and colleagues reported 92% local control for 13 patients who received median EBRT dose of 59.4 Gy postoperative radiation therapy after a median follow-up of 3.7 years (Komotar et al. 2012).

A few series have suggested that dose escalation above 60 Gy dramatically increases local control and survival. Hug and colleagues utilized photons, protons, or a combination of photons and protons for treatment of 31 patients with WHO grade II and III meningiomas (Hug et al. 2000). For the subgroup with malignant meningioma, improved local control corresponded with improved overall survival. They reported three patients had symptomatic radiation damage. Boskos and colleagues also utilized combined photons and protons to treat 24 patients with high-grade meningiomas (79% grade II)

typically following STR. They reported cause-specific survival at 5 years of 80% with greater than 60 Gy compared with 24% with less than 60 Gy (p = 0.01). There was a trend toward further improvement with doses greater than 65 Gy (p = 0.06) (Boskos et al. 2009). They reported just one patient had radionecrosis.

Indeed, though dose escalation clearly improves local control rates, a concern for increasing rates of radionecrosis must be balanced with this improvement. Katz and colleagues reported on accelerated hyperfractionated radiation therapy (60 Gy at 1.5 Gy per fraction twice daily ± radiosurgery boost) and found no benefit with unacceptable toxicity (Katz et al. 2005). Techniques such as IMRT or proton therapy may allow dose escalation by improving the conformality of the target and volume of irradiated brain. In addition, further improvements in functional imaging may allow us to better target residual disease for selective dose escalation.

Two trials recently completed accrual and may help to answer our questions about the appropriate dose. RTOG-0539 trial used 54 Gy in 30 fractions for newly diagnosed atypical meningioma following GTR and 60 Gy in 30 fractions following STR or for recurrent grade II tumors of any resection extent. EORTC 22042–26042 employed 60 Gy following a GTR and added a 10 Gy boost after STR for atypical and malignant meningiomas.

2 Vestibular Schwannoma

Vestibular schwannomas (VS) represent the second most common benign intracranial tumor after meningioma. They are typically slow-growing intracranial, extra-axial tumors arising from the Schwann cells surrounding the eighth cranial nerve. Their incidence is approximately 1–2 in 100,000 with increasing detection of otherwise asymptomatic lesions in the modern era as a result of incidental findings on MRI scans (Fortnum et al. 2009). The median age of diagnosis is in the mid 50s, and more than 90% of all tumors are unilateral with exception of those bilateral tumors presenting as a manifestation of neurofibromatosis type 2 syndrome (Howitz et al. 2000; Lanser et al. 1992). When symptomatic, patients diagnosed with vestibular schwannomas typically present with hearing loss, dizziness, tinnitus, or more rarely with nerve palsies involving the trigeminal and facial nerves. Although pathologically benign, given their location, these tumors can cause symptomatic morbidity due to local mass effect, with compression of adjacent cranial nerves or brainstem, and potential development of hydrocephalus. Given their tendency to grow, even small or asymptomatic tumors can progress to debilitating symptoms in young or otherwise healthy patients.

2.1 Active Surveillance Versus Treatment

Treatment strategies differ based on a number of factors including age and performance status of the patient, size of the lesion, and patient preferences. In general, the strategies for managing VS range from simple observation to microsurgical resection or radiation therapy using stereotactic localization. VS tend to grow slowly (Battaglia et al. 2006), with an average growth rate of only 1–2 mm per year making observation alone with serial MRI an appropriate initial management strategy for minimally symptomatic tumors incidentally identified, especially in older patients (Flint et al. 2005; Glasscock et al. 1997; Hajioff et al. 2008; Hoistad et al. 2001). In a series of 729 patients allocated to observation, only 17% of intrameatal tumors grew outside of the meatus, and 30% of tumors with extrameatal extension grew more than 2 mm with a mean observation time of 3.6 years (Stangerup et al. 2006). Since treatment with either surgery or radiation therapy is associated with risk of hearing loss and small but real risk of other cranial nerve deficits, active surveillance may be the best strategy.

On the other hand, tumor progression may have important consequences, including hearing loss and the inability to consider multiple therapeutic options. It has been suggested that tumor growth may lead to a loss of eligibility for hearing preservation surgery in up to 30%

of patients (Flint et al. 2005; Shin et al. 2000). A number of studies have demonstrated deterioration in hearing function with observation, even in the absence of tumor growth (Hajioff et al. 2008; Stangerup et al. 2008), and consequently, in those patients with functional hearing who are otherwise candidates for treatment, active management has been recommended. Unfortunately, there are no clear stratification factors that identify those patients likely to undergo tumor progression or develop symptoms, and further studies into the identification of ideal candidates for active surveillance are still necessary.

2.2 Surgery Versus Radiosurgery

Surgical management of VS has historically been the backbone of therapy with the ultimate goal of complete resection of the tumor. Continuous refinement of surgical techniques over the past decades has reduced operative mortality to less than 1% and has led to reductions in morbidity due to surgically induced cranial nerve dysfunction, cerebrospinal fluid leakage, wound infection, and deep vein thrombosis (Ebersold et al. 1992). Nonetheless, operative management of patients with VS may lead to abnormal facial function. The risk of facial nerve complications varies depending on the size of the tumor and individual series, but for small tumors has been reported as less than 5–10% (Gormley et al. 1997; Samii and Matthies 1997).

Since the first patient was treated with the Leksell Gamma Knife in 1969, various modalities of radiation therapy have been increasingly utilized to treat VS. These approaches include SRS, proton beam radiation therapy, and conventional fractionated intensity-modulated X-ray radiation therapy (IMRT). There is accumulating evidence that radiation therapy offers excellent tumor control in a majority of cases, with relatively few side effects, and may be an excellent option for many patients. Unfortunately there is still a lack of solid level 1–2 evidence in the form of randomized controlled trials to guide practitioners in the optimal treatment strategy for these patients, and the best management of patients with small moderate-sized vestibular schwannoma remains controversial (Kaylie et al. 2000; Pollock et al. 1998; Sekhar et al. 1996).

Given this dearth of definitive evidence to guide practitioners in counseling patients, a number of recent publications have addressed the controversy through meta-analyses, single-institution studies, and long-term observational trials. A comprehensive review of the published literature published in 2002 reviewed 111 studies reporting outcomes after management of VS using primarily surgery and SRS (Nikolopoulos and O'Donoghue 2002). The authors concluded that the published literature supporting various methods of managing VS was generally of low quality type 3 and 4 evidence and that there was no level 1–2 evidence to guide practitioners.

In general, tumor control with both approaches is thought to be quite good, with greater than 90% of patients having long-term control of their tumor when modern techniques are utilized. A confounding factor limiting the conclusions that can be drawn about long-term VS control after SRS is the high doses historically used for treating these tumors, generally in excess of what is used today (Kondziolka et al. 1998). Recently, however, outcomes were reported for 317 VS patients treated between 1991 and 1998 to a mean dose of 13.2 Gy at tumor margin (Hasegawa et al. 2005a, b). The 10-year progression-free survival in this group was 97% for patients with tumors less than 15 cc, suggesting that even lower doses are effective for treatment of VS, with good long-term control. Given the good tumor control attainable using surgery or SRS, major differences between these techniques may arise only when secondary outcomes such as hearing preservation, trigeminal neuralgia, and facial nerve dysfunction are considered. A number of studies have assessed these functional endpoints and can provide some guidance to clinicians.

One meta-analysis of studies comparing tumors <4 cm treated with surgery or SRS reported no significant difference in hearing preservation or facial nerve dysfunction between treatment groups (Kaylie et al. 2000). In these

patients, hearing preservation rates were 44% in both groups, which is lower than results in other papers assessing functional outcomes after SRS. This publication included patient data back to the 1960s, was complicated by inconsistent data reporting, and reported a mean treatment dose higher than modern treatment protocol doses of 12–15 Gy. The authors noted higher complications and increased morbidity with SRS when compared to surgery, so it is possible that the high SRS doses used contributed to these adverse outcomes. The authors concluded that surgery demonstrated superior tumor control over Gamma Knife SRS, but acknowledge that recurrence after surgery is likely underreported in the literature they included, and noted that their included surgical data did not routinely use longitudinal imaging to monitor true rates of tumor recurrence (Kaylie et al. 2000).

More recently, another meta-analysis compared the reported outcomes of small VS (<2 cm) treated with microsurgery or SRS (Maniakas and Saliba 2012). Their analysis included 1292 patients from 16 studies dating between 1979 and 2011, with inclusion criteria of a minimum 5-year follow-up. Nearly all the SRS patients were treated with Gamma Knife, aside from 29 patients treated with LINAC-based SRS. The authors reported similar long-term tumor control in both techniques, with median 8-year tumor control of 96% after SRS and 7-year tumor control of 98% after microsurgery. Unlike the results reported by Kaylie et al., these authors reported significant improvement in hearing preservation following SRS when compared to microsurgery. Useful hearing preservation in SRS patients was reported in 70.2% of cases with a 6.9-year follow-up; there were however no reported cases of hearing improvement in any patients treated with SRS. In contrast, surgical hearing preservation was 50.3%, with a mean follow-up of 7.14 years. 6.5% of patients managed surgically reported hearing improvement with a long-term follow-up. Facial and trigeminal neuropathies were uncommon with either technique, occurring in up to 3.1% of patients treated with SRS and 5.3% of patients after surgical intervention.

Aside from differences in the duration of follow-up and the date ranges of the studies included, a major difference between these two meta-analyses was the sizes of the included tumors. The earlier study included tumors up to 4 cm, while the more recent publication limited tumor size to <2 cm. It is possible that the differences seen between rates of hearing preservation after SRS can be attributed to differences in tumor size, with larger lesions resulting in less successful hearing preservation after SRS. This finding would be consistent with studies which looked at this parameter in surgical series (Umezu and Aiba 1994; Hecht et al. 1997; Satar et al. 2003) and found a correlation between larger tumors and reductions in functional hearing preservation after resection. Interestingly, however, a recent report assessed GK SRS outcomes in patients with tumors including those greater than 3 cm, and no significant difference in hearing preservation was found when assessing tumors based upon size, though overall rates of hearing preservation were only 51% in this study population (Yang et al. 2010a).

A recent single-institution cohort study by Pollock et al. compared microsurgical resection with stereotactic radiosurgery in 82 patients with unilateral VS measuring less than 3 cm (Pollock et al. 2006). Primary outcomes included assessment of facial function, and rates of hearing preservation, with a mean follow-up of 42 months. When compared to surgical resection, facial movement overall was significantly better in the SRS group at 3 months (100% vs. 61%), 1 year (100% vs. 69%), and at last follow-up (96% vs. 75%). Similarly, hearing preservation was better following SRS at all time points. AAO-HNS Class A or B hearing was present in 77% vs. 5% at 3 months favoring SRS. The same rates were 63% vs. 5% at 1 year as well as at last follow-up. When only Class A hearing was considered, rates were 56% vs. 0% in favor of SRS at 3 months and 50% vs. 0% at 1 year as well as at last follow-up. Of note, two patients with Class C or D hearing in the SRS group improved to Class B hearing at last follow-up.

The positive SRS outcomes reported by Pollock et al. are generally in concordance with a

number of other comparisons of SRS and surgery for management of VS. At least five retrospective studies have compared the two approaches, and all of these studies found better hearing preservation and improved facial nerve outcomes following SRS (Karpinos et al. 2002; Myrseth et al. 2005; Pollock et al. 1995; Regis et al. 2002; van Roijen et al. 1997). Although longer term study of lower dose SRS for VS is needed to establish efficacy, early studies are promising that the functional outcomes of SRS may be superior to those of surgery, at least in patients with small tumors. When combined with the findings of a number of large SRS series that suggest the need for resection following radiosurgery may be less than 3% (Kondziolka et al. 1998; Hasegawa et al. 2005a; Flickinger et al. 2004; Foote et al. 2001; Petit et al. 2001), there is general support for the conclusion that SRS affords good tumor control with excellent functional outcomes and can represent a great alternative to more invasive surgery in patients with vestibular schwannomas.

2.3 Fractionation

Though the majority of studies concentrate on single-session SRS for vestibular schwannoma, advances in technology have enabled the implementation of stereotactic radiosurgical methodologies using noninvasive immobilization methods. Subsequently, various protocols to treat VS using stereotactic radiation therapy have been described, with schedules ranging from 4 to 32 fractions (Andrews et al. 2001; Meijer et al. 2000; Poen et al. 1999; Szumacher et al. 2002; Fuss et al. 2000; Lederman et al. 1997; Combs et al., 2005). Radiobiologic models suggest a direct correlation between late toxicity and fractional dose size, with reductions in fractional dose generally leading to reductions in morbidity over time (Larson et al. 1993; Marks 1993). One potential benefit of fractionation for the treatment of VS, therefore, may be the reduction of toxicity when compared with microsurgery or single-fraction radiosurgery. It is unclear whether morbidity can be reduced while maintaining the excellent tumor control obtainable using radiosurgery. Indeed, a number of studies have suggested comparable control rates with minimization of the morbidity associated with single-dose radiosurgery (Fuss et al. 2000; Lederman et al. 1997), but many of these studies lack sufficient long-term follow-up.

In one single-institution study, 125 patients were treated with either single-session Gamma Knife SRS or LINAC-based radiation therapy to a dose of 50 Gy in 2 Gy fractions. All patients demonstrated serviceable hearing at baseline and were treated with SRS versus LINAC-based SRT according to physician preference. Follow-up included serial MRI scans, neurologic examinations, and audiometry; trigeminal nerve and facial nerve function was also assessed in follow-up. The study found posttreatment serviceable hearing after SRS in 33% of patients treated. In contrast, in this study serviceable hearing was maintained in 81% of patients undergoing treatment with fractionated SRT. Unfortunately, this study was somewhat limited by a relatively short outcomes reporting at 1 year, which may be too early to assess true tumor control. Furthermore, the reported hearing preservation after SRS in this study is at the low end of other published series, which range from 39–67% of patients with posttreatment serviceable hearing (Flickinger et al. 1996; Miller et al. 1999; Thomassin et al. 1998; Subach et al. 1999). Nonetheless, assuming long-term control after fractionated SRT may be equivalent to single-session SRS, there is reason to be optimistic that fractionation may reduce subsequent cranial nerve deficits in these patients, an outcome which would be in keeping with current radiobiological theory and is supported by a number of recent publications (Foote et al. 2001; Suh et al. 2000; Mendenhall et al. 1996).

Another single-institution publication reporting on long-term outcomes following fractionated radiation therapy for treatment of vestibular schwannoma assessed 106 patients treated with 57.6 Gy in 1.8 Gy fractions with a median follow-up time of 48.5 months. Outcomes included actuarial local tumor control rates of 94.3% at 3 years and 93% at 5 years after fractionated SRT. This study reported useful hearing preservation rates of 94% at 5 years and noted that there was a dramatic difference between patients with

neurofibromatosis, with resulting reductions in hearing preservation. The authors reported that hearing preservation in non-NF 2 afflicted individuals was 98% at 5 years, while those with NF 2 had hearing preservation rates of 64%. As with other modern studies, the rates of other cranial nerve toxicities were rare, with trigeminal and facial nerve dysfunction rates of 3.4% and 2.3%, respectively (Combs et al. 2005).

In addition, multiple series have examined hypofractionated radiation therapy schedules, which may represent a middle ground between standard fractionation and single-session SRS. Stanford published on 383 patients treated with 18 Gy in three fractions with CyberKnife hypofractionated radiation therapy, after a median follow-up of 4.6 years, the tumor control rate was 96% at 5 years and 98% for tumors less than 3.4 cm^3 (Hansasuta et al. 2011). Of the 200 patients with Gardner-Robertson grade 1 and 2 hearing, the hearing preservation was 76%. Utilizing LINAC-based hypofractionated stereotactic radiation therapy, Johns Hopkins published on 496 patients treated between 1995 and 2007 with 25 Gy in five fractions (or 30 Gy in ten fractions for 11% of the patients). Of 385 patients with at least 18-month follow-up, 3% required salvage surgery; however, 30% had radiological progression (Kapoor et al. 2011).

Despite the possible radiobiological benefits from fractionation, the lack of long-term data has caused some to question whether fractionated treatment will be associated with similar long-term control as single-session radiosurgery (Linskey 2013). This is especially concerning given schwannomas are late responding tumors with a low proliferative index and alpha-beta ratio. In addition, hearing preservation after SRS likely depends on the dose to the cochlea (Yomo et al. 2012; Kano et al. 2013), as different immobilization techniques and radiosurgery devices allow for varied levels of conformality and avoidance of the cochlea and cochlear nerve. Thus, if platforms for single-session radiosurgery afford better precision and conformality, radiosurgery may have superior outcomes than a fractionated radiation therapy platform that involves more radiation dose to the objects at risk.

The high rates of tumor control achievable using modern radiation therapy techniques represent an exciting transition away from the need for morbid operative procedures in patients diagnosed with vestibular schwannoma. The optimal management strategies remain to be determined however, and questions regarding the best methods for achieving long-term tumor control while minimizing treatment-related morbidity remain incompletely resolved. With continued long-term follow-up of these patients, factors including tumor size, NF 2 status, tumor location, and baseline symptoms at presentation may be used for development of nomograms outlining optimal management strategies encompassing all available radiation therapy techniques.

3 Pituitary Adenomas

Pituitary adenomas account for 10% of all intracranial neoplasms and are the most common sellar mass from the third decade on. They are benign tumors of the anterior pituitary and classified by size and cell of origin. Lesions smaller than 1 cm are classified as microadenomas, while lesions larger than 1 cm are classified as macroadenomas. Either may cause symptoms as a result of increased hormone secretion produced by the cell of origin. Gonadotroph adenomas generally present as clinically nonfunctioning sellar masses. Thyrotroph adenomas may present as clinically nonfunctioning sellar masses that secrete only alpha or TSHB subunits or may cause hyperthyroidism due to increased secretion of intact thyroid-stimulating hormone. Corticotroph adenomas often cause Cushing's disease. Lactotroph adenomas usually cause hyperprolactinemia, which leads to hypogonadism in women and men. Somatotroph adenomas associated with increased growth hormone secretion cause acromegaly. Mixed cell adenomas also exist, but are less common. In addition, pituitary adenomas may cause symptoms by mass effect (vision impairment and headaches) or due to compression of other cell types causing decreased secretion of other hormones.

Transsphenoidal surgery is the mainstay of treatment for pituitary adenomas, and advancements in

surgical techniques have minimized complications in the hands of an experienced neurosurgeon. Medical management is also central to the treatment of secretory pituitary adenomas, for instance, patients with lactotroph adenomas are most often treated with a dopamine agonist initially, regardless of the size of the adenoma. Radiation therapy plays an important role in the management of pituitary adenomas that are incompletely resected, have recurred biochemically or radiographically, and are at high risk for recurrences despite surgical resection or in the case of a medical inoperable patient. However, there remains controversy over when to use radiation therapy, the best fractionation schedule, and the rates of hypopituitarism that results.

3.1 Nonfunctioning Pituitary Adenoma

Standard fractionated external beam irradiation was first utilized for treatment of pituitary adenomas with good local control rates at 45–50.4 Gy (Colin et al. 2005; Ronson et al. 2006). However, SRS is now the preferred technique as it has shown comparable local control rates and is given in a single session as opposed to 5–6 weeks (Pollock et al. 2008; Voges et al. 2006). A single fraction is not always safe if the tumor is too large or close to critical normal structures including the optic apparatus and brainstem. Standard fractionation in these cases minimizes the risk of late complications of these normal structures.

The late effects of radiation therapy are important to consider in patients with nonfunctioning pituitary adenoma, since the vast majority are cured. Thus there is controversy whether to treat nonfunctioning adenomas after subtotal resection or follow active surveillance. After surgery alone for nonfunctioning pituitary adenoma, approximately 50% of subtotally resected tumors and 10–25% of gross totally resected adenomas progress at 10 years (Brochier et al. 2010; Losa et al. 2008; van den Bergh et al. 2007; Dekkers et al. 2006; Greenman et al. 2003; Turner et al. 1999). Gittoes and colleagues published a comparative retrospective series of 126 patients treated at two hospitals; one hospital routinely offered postoperative radiation therapy to 45 Gy and the other did not. The progression-free survival was 93% with radiation therapy versus 33% without ($p < 0.05$) (Gittoes et al. 1998). This improvement in PFS was confirmed in other series, but there was no difference in life expectancy or pituitary function (van den Bergh et al. 2007).

3.2 Functioning Pituitary Adenoma

Success of radiation therapy in controlling tumor growth is over 90% in most series regardless of the radiation technique or adenoma subtype. However, for hormone-secreting adenomas, the rate and timing of biochemical normalization greatly vary among series given different patient populations, radiation techniques, doses, and definitions of biochemical normalization (Sheehan et al. 2005). Rates of biochemical response are greatly influenced by the histology as well as other available treatments (Zierhut et al. 1995; Minniti et al. 2007; Estrada et al. 1997). For instance, success in achieving remission for prolactinomas appears to be quite poor compared to other adenoma subtypes with biochemical remission occurring in only 15–30% of cases with radiation therapy alone and often requires a latency of several years (Sheehan et al. 2005; Littley et al. 1991). However, given the small number of cases, these poor outcomes may also reflect the selection of the few patients refractory to medical and surgical management.

For Cushing's disease, both standard fractionated RT and SRS achieve biochemical remission rates (typically defined as normalization of urinary free cortisol and serum ACTH) of 50–80% (Estrada et al. 1997; Sheehan et al. 2000; Petit et al. 2008). For treatment of acromegaly, rates of biochemical remission are reported over a large range from 17% to 96% (Castinetti et al. 2005; Kobayashi et al. 2005; Petit et al. 2007; Zhang et al. 2000). This not only reflects different patient populations but also a wide range of definitions for response, with the most common definition being normalization of IGF-1 and growth

hormone level <1 ng/mL after glucose challenge. In addition, the length of follow-up varied in the series and many patients do not respond until many years after treatment.

For functioning adenomas, SRS is preferred because biochemical normalization following radiosurgery is reached more quickly than following fractionated radiation therapy (Sheehan et al. 2005; Landolt et al. 1998; Mitsumori et al. 1998). For example, Landolt and colleagues published on 66 patients treated for acromegaly. Among 16 patients who underwent SRS to 25 Gy to the 50% isodose surface, the mean time to normalization was 1.4 years compared to 7.1 years among the remaining 50 patients treated with fractionated radiation therapy to 40 Gy. A meta-analysis by Dabrh and colleagues found 30 eligible studies assessing 2464 patients treated with SRS or EBRT for acromegaly (Abu Dabrh et al. 2015). There was a nonsignificant increase in remission rate at latest follow-up (52% vs. 36%; $p = 0.14$) and significantly lower follow-up IGF-1 level (−409.72 ug/L vs. −102 ug/L; $p = 0.002$). There was a lower rate of hypopituitarism (32% versus 51%; $p = 0.05$) with SRS. However, this meta-analysis did not account for selection bias, and it is likely that the patients receiving EBRT had larger tumors, closer to the optic structures. Overall, SRS is preferred for functioning pituitary adenomas, but when the size or location of the optic apparatus is associated with a high risk to vision, standard fractionated or hypofractionated stereotactic radiation therapy should be utilized.

Lastly, several retrospective series have also shown that concurrent use of pharmacotherapy while receiving radiation therapy leads to poorer rates of biochemical response (Sheehan et al. 2011; Castinetti et al. 2007; Pollock et al. 2007). This has led to many experts recommending that medical therapy be held a month prior to radiation therapy in an effort to improve biochemical response.

3.3 Rate of Hypopituitarism

The risk of new hypopituitarism after radiation therapy has also been variably reported given diverse techniques and follow-up periods. Overall the risk of affecting at least one axis is 20–60% at 5 years after fractionated radiation therapy or SRS (Minniti et al. 2007; Estrada et al. 1997; Sheehan et al. 2000; Hoybye et al. 2001). However, with longer follow-up, the estimated rate increases, and Minnitti et al. reported new hypopituitarism in 85% of patients at 15 years (Minniti et al. 2007). Many think that with enough time, development of hypopituitarism is inevitable after radiation therapy. However, dosimetric data suggest that avoidance of dose to the normal gland reduces the risk of hypopituitarism (Leenstra et al. 2010). Furthermore, as would be expected, smaller tumors are also associated with lower rates of hypopituitarism (Pollock et al. 2008). As advances in imaging and delivery systems have occurred, many have moved from treating the whole sella to just visible tumor. It remains to be seen if the risk of hypopituitarism decreases with longer follow-up of modern treatment techniques.

4 Craniopharyngioma

Craniopharyngiomas are rare, benign tumors that arise from remnants of Rathke's pouch. They can be solid or mixed solid-cystic tumors. Patients with craniopharyngioma have a bimodal age distribution with one peak in children between 5 and 14 years and a second peak in adults between 50 and 75 years (Bunin et al. 1997). With treatment, most patients are cured. However, given its location in the sellar and suprasellar region near critical neural and vascular structures, both tumor growth and intervention cause morbidity. A Swedish population-based study of 307 patients with craniopharyngioma followed for a median of 9 years showed that individuals with craniopharyngioma had a three- to fivefold increase in expected mortality compared with the general population (Olsson et al. 2015). The major contributors to excess mortality could be related to treatment morbidity, including cerebrovascular disease, type 2 diabetes mellitus, myocardial infarction, and severe infection.

Given the morbidity of treatment despite good local control rates, the initial therapy of

craniopharyngioma continues to be the subject of considerable controversy. Though most established algorithms advocate for gross total resection (GTR) or subtotal resection (STR) followed by radiation therapy, many patients are treated with other strategies (Hankinson et al. 2012, 2013). These include observation, radiation therapy alone, subtotal resection alone, stereotactic radiosurgery, and intracystic therapies.

4.1 Extent of Surgery

For many years, GTR was felt to be the treatment of choice, as it had better rates of tumor control compared to STR alone and allowed for avoidance radiation therapy in young patients. However, aggressive surgical resection is often associated with endocrinologic and behavioral morbidity. This has caused some to advocate a strategy of neural decompression by cyst drainage and limited solid tumor resection followed by radiation therapy. Still, others argue that initial GTR is the best chance for surgical cure and can be accomplished with acceptable morbidity.

The University of California San Francisco group has published a meta-analysis of 442 patients who underwent resection for craniopharyngioma, including GTR for 58% of the cases, STR for 23%, and STR + RT for 19%. The 2- and 5-year progression-free survival rates for the GTR group versus the STR + RT group were 88 versus 91% and 67 versus 69%, respectively. The 5- and 10-year OS rates for the GTR group versus the STR + RT group were 98 versus 99% and 98 versus 95%, respectively (Yang et al. 2010b). The differences were not statistically significant and reflect the excellent disease control outcomes also published in single-institution series.

The same group used the available data to compare the side effects of GTR versus STR for treatment of craniopharyngioma. They found small numbers of patients (mean 5.8, range 1–45) in individual series on the treatment of craniopharyngioma and overall felt that toxicity was underreported. There was no statistically significant difference in the rate of neurologic deficits between patients receiving GTR alone, STR alone, or STR + RT (6.9 vs. 4.2 vs. 1.8%) in univariate analysis, but on multivariate analysis controlling for study size, they did find a statistically increased risk of neurologic deficits for GTR compared to STR + RT (Sughrue et al. 2011). GTR was associated with a 2.5 times greater risk of at least one endocrinopathy compared to patients with STR + RT (52% versus 20%, $p < 0.000001$). Visual decline was low overall, at 3.5% after GTR versus 6.4% with STR and RT ($p = 0.11$).

4.2 Timing of Radiation Therapy

Many series have shown that adjuvant RT improves progression-free survival (Karavitaki et al. 2005). However, it is not clear that adjuvant RT improves overall survival when compared with active surveillance and only salvage RT if needed. The University of Pennsylvania reviewed 75 patients treated for craniopharyngioma at their institution over a 27-year period (Stripp et al. 2004). All patients underwent an attempt at GTR. Adjuvant RT was given to 18 of the 27 patients in whom only an STR was possible and to 22 patients who had relapse after GTR. Though local control was superior for patients who received STR + RT versus those who had surgery alone (42% vs. 84%, respectively; $p = 0.004$), the overall survival for the entire cohort was 85%.

Since a large proportion of patients after STR will require RT and with tumor progression, patients can have visual or endocrinologic compromise, many recommend adjuvant RT after STR. However, craniopharyngioma patients are at risk for many late effects of radiation therapy given that they are often young and have a good prognosis. The tumor location lends itself to risk of hypopituitarism, visual deficits, neurocognitive decline, and vascular effects. Given this and the efficacy of salvage RT, others will observe and only pursue RT on progression.

4.3 Radiation Technique

To address late effects, radiation oncologists have used technological advances in imaging and radiation

delivery to obtain greater treatment precision and conformity. Various techniques have been utilized to decrease long-term toxicity by limiting the exposure of surrounding normal tissues to ionizing radiation. Stereotactic techniques utilizing stable frame systems and establishing patient-specific coordinate systems have been used for standard fractionation to improve precision and allow for smaller margins added for setup uncertainty (Minniti et al. 2009; Harrabi et al. 2014). In addition, planning techniques such as IMRT have been used to spare dose to the adjacent brain and optic apparati with good long-term disease control despite initial concerns that more precise targeting would be detrimental given ill-defined target volumes after surgical interventions and dynamic cyst volume changes during radiation therapy (Greenfield et al. 2015).

With increasing availability, proton therapy has also been advocated for treatment of craniopharyngioma as proton plans are associated with reduced integral dose to structures associated with neurocognition, optic chiasm, and cochleae compared to IMRT (Boehling et al. 2012; Beltran et al. 2012). MD Anderson and Baylor compared outcomes from 52 children treated between 1996 and 2012 with proton beam therapy or photon IMRT. There was no difference in OS or disease control. OS, nodular failure-free survival, and cystic failure-free survival at 3 years were 96%, 95%, and 76%, respectively. During therapy, 40% had cyst growth with 20% requiring surgical intervention. Similarly, 33% and 27% had immediate or late cyst growth after treatment, with intervention required in 40% (Bishop et al. 2014). This experience emphasizes the importance of monitoring for cyst growth during treatment in case intervention or replanning of radiation therapy is required (Winkfield et al. 2009).

SRS in a single session has also been used for small tumors with comparable local control rates. The Pittsburgh group published on 46 patients with craniopharyngioma who underwent 51 courses of treatment with SRS for residual or recurrent tumor (Niranjan et al. 2010). The tumor volume was small (1.0 cm3; range 0.07–8.0 cm3). At a mean follow-up of over 5 years, the 5-year overall and progression-free survival rates were 97% and 92%, respectively. The overall local control rate (for both solid tumor and cyst control) was 81% and 68% at 3 and 5 years, respectively. No patients with normal pituitary function developed hypopituitarism after SRS.

5 Glomus Jugulare Tumors

Glomus jugulare (GJ) tumors, also known as chemodectomas, are paragangliomas arising from neural crest cells within the autonomic ganglia of the jugular bulb. In the modern era of increased medical imaging, incidental findings of glomus tumors are increasing, and in asymptomatic or elderly individuals, observation alone may be appropriate (Carlson et al. 2015). Although benign, these rare and slow-growing tumors can cause a number of problems secondary to mass effect or invasion of neurovascular structures, which may result in symptoms such as pain, dizziness, visual changes, facial droop, Horner's syndrome, and/or hoarseness. On rare occasions they can also be functional tumors, with secreted catecholamines leading to labile blood pressure and tachycardia (Chretien et al. 1971). In the setting of symptomatic presentation, intervention is warranted.

The treatment options for GJ include embolization and surgical resection, or radiation therapy using either conventional or hypofractionated external beam approaches, or stereotactic radiosurgery. Given the rarity of these tumors, a variety of treatment paradigms are currently used, and there is no general consensus regarding optimal management to control tumor burden while minimizing treatment-related morbidity. Due to their location and relative inaccessibility, as well as the highly vascular nature of GJ, surgical excision is often problematic and continues to pose significant challenges despite improvement of modern techniques (Springate et al. 1991; Ojemann 1992; Netterville and Civantos 1993). Complications after surgery may include lower cranial nerve deficits, CSF leak, wound infection, and thromboembolic events (Gottfried et al. 2004). A recently published modern series of 34 patients managed surgically between 1997 and 2007, with a mean follow-up time of 52 months resulted in a tumor control rate of 94.2%, with

17.6% of patients developing lower cranial nerve deficit after surgery and 17.6% of patients developing cerebrospinal fluid leaks (Borba et al. 2010).

Conventional external beam radiation therapy techniques were first applied to manage GJ tumors in the 1950s, but were less than optimal due to the requirement for large treatment planning margins and associated morbidities (Chretien et al. 1971). Improvement in external beam radiation therapy techniques, including the use of three-dimensional planning, allowed for reduction in margins, and a review published in 1990 demonstrated that conventionally fractionated external beam radiation therapy resulted in equivalent control rates when compared to surgery, with reductions in treatment-associated morbidity compared to operative management (Springate and Weichselbaum 1990). Unfortunately, owing to the rarity of GJ tumors, there are no randomized controlled trials comparing various treatment strategies.

More recently, Gamma Knife SRS (GKS) has been successfully utilized for management of GJ tumors, with good outcomes, including durable tumor control and minimal side effects in a well-tolerated, relatively noninvasive, outpatient procedure (Kida et al. 1995). Alternative techniques for radiosurgery of GJ tumors using LINAC or CyberKnife (CK) approaches are also increasing in frequency. Irrespective of the technique used, benefits of SRS include excellent precision and accuracy with rapid dose falloff outside the target area. A recently published meta-analysis of retrospective data of the radiosurgical management of GJ tumors in over 300 patients found that 97% of patients treated with SRS using GKS, CK, or LINAC-based techniques achieved tumor control according to imaging criteria and furthermore found that 95% of patients were either stable or improved clinically after SRS (Guss et al. 2011). Patients treated with LINAC and CK fared slightly better overall, with 97% of patients improving clinically (Guss et al. 2011). Another recent meta-analysis identified 869 patients historically treated with surgery, SRS, or combination therapy in the case of subtotal resection and reported on aggregate outcomes in these patients. Although this publication was somewhat limited by the quality of the source literature, findings were consistent with the outcomes reported by Guss et al., with 95% of patients in the SRS group achieving tumor control during the study period (Ivan et al. 2011). Surgical tumor control ranged from 69% to 86% depending on the extent of resection, an insignificant difference but showing a trend toward improved tumor control with attainment of GTR (Ivan et al. 2011). Importantly, pooled analysis of the risk of CN deficits after treatment showed approximately two- to fourfold increased risk with surgery, although limitations regarding length of follow-up and standardized reporting of these symptoms certainly limit the conclusions that can be drawn.

The controversies surrounding the optimal management of glomus jugulare tumors are likely to persist given the relative indolence and rarity of these tumors. In the absence of definitive level I evidence, single-institution studies and meta-analysis of these publications can provide some guidance in the management of these patients, but are limited by inconsistent outcomes reporting and short follow-up. Given the technical difficulties of surgery and the relative morbidity of operative management, there has been interest in utilization of radiation therapy for primary tumor control. Outcome data regarding tumor control following SRS, CK, or LINAC-based radiosurgery is reassuring, but may be limited by length of follow-up. With the advent of SRS techniques and modern medical imaging guidance, the morbidity of radiation therapy is dropping in the modern era. A better understanding of stratification factors such as tumor size, presenting symptom, and factors determining tumor stage will ultimately be necessary for the optimal management of these patients.

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Lymphoma

Colette J. Shen and Stephanie A. Terezakis

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Abstract

While radiation therapy alone was historically used in the early management of both Hodgkin and non-Hodgkin lymphoma, the advent of effective systemic therapy shifted the treatment paradigm toward combined modality therapy. Despite substantial evidence establishing the importance of radiation therapy in local control for both Hodgkin and non-Hodgkin lymphoma, controversy surrounding its use in certain patient populations still exists, in large part, because of concerns of late toxicity resulting in morbidity and mortality in lymphoma survivors. In response, significant efforts have been made to refine the delivery of radiation therapy in the combined modality setting such that toxicity is minimized while still preserving disease control. Advances in imaging and treatment delivery, including use of 3D conformal therapy, intensity-modulated radiation therapy, and proton therapy, have allowed for more conformal radiotherapy delivered to smaller fields with lower doses. At the same time, efforts to identify which patients would benefit most from radiation therapy, using risk stratification and response-based assessment, are providing further guidance on the development of individually tailored treatment regimens that incorporate radiotherapy in the most beneficial manner. Continued investigation on radiation field size, dose, and advanced delivery techniques is needed to ensure clinical efficacy is not compromised with treatment de-intensification and increased conformality.

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1 Introduction

Prior to the development of effective chemotherapy regimens, radiation therapy (RT) alone was used in the definitive management of both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). However, this approach required large treatment fields that exposed significant volumes of normal tissue to high radiation doses. As a result, late toxicities, in particular secondary malignancies and cardiopulmonary disease, contributed substantially to morbidity and mortality in lymphoma survivors. With the introduction of effective chemotherapy regimens that could target subclinical disease, the treatment paradigm for both HL and NHL shifted toward combined modality therapy, allowing for delivery of lower RT doses with smaller treatment fields without compromising disease control (Ansell 2015a, b; Meyer and Hoppe 2012; Zietman 2015). As control rates are now excellent with combined modality therapy, the focus has shifted toward tailoring and de-intensifying treatments when possible to minimize treatment-related toxicity. Advances in imaging techniques, along with RT planning and delivery systems, have spurred efforts to identify patients who will benefit most from RT and to limit exposure of normal tissues to RT even further.

2 Hodgkin Lymphoma

No effective treatment existed for HL for decades following its discovery in 1832, until X-ray therapy began to be used in the early 1900s. Five-year survival reached 50 % with the use of larger field sizes in the 1950s (Hoppe 2013). However, the introduction of effective chemotherapy in the 1960s, with responses achieved first to mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) and then doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimens, resulted in a shift from extensive RT only to combined modality treatment with lower RT doses (Ansell 2015a; Meyer and Hoppe 2012; Zietman 2015). With the majority of patients achieving long-term survival, the focus has shifted toward minimizing unnecessary treatments and associated toxicity, tailoring treatments based on individual risk factors and limiting RT fields.

2.1 Role of Radiation Therapy

2.1.1 Early-Stage Hodgkin Lymphoma

The role of RT in the treatment of early-stage HL is controversial despite evidence supporting a reduced risk of relapse with RT (Thomas et al. 2007; Meyer et al. 2005, 2012; Herbst et al. 2011). The primary concern with RT is that any impact on overall survival (OS), due to the improvement in progression-free survival (PFS), may be potentially outweighed by the many treatment-related deaths occurring decades after RT from late effects, such as cardiovascular complications and secondary malignancies. Indeed, despite the clear benefit conferred by RT in reducing risk of relapse, prospective studies comparing chemotherapy to combined modality therapy using modern chemotherapy regimens and RT techniques have not clearly demonstrated a statistically significant OS advantage (Meyer et al. 2005, 2012; Straus et al. 2004; Kung et al. 2006). This is in part due to the high salvage rate in patients who relapse and the development of treatment-related late complications seen at longer follow-up beyond a decade. Nevertheless, the benefit of RT depends on individual risk factors such as stage, presence of bulk, and response to therapy (Ansell 2015a; Meyer and Hoppe 2012; Herbst et al. 2011; Crump et al. 2015; Terezakis and Hoppe 2012).

The National Cancer Institute of Canada (NCIC)–Eastern Cooperative Oncology Group (ECOG) HD6 trial analyzed patients with non-bulky, stage IA–IIA HL (Meyer et al. 2005, 2012) and evaluated efficacy and toxicity of ABVD chemotherapy-alone versus radiation-based therapy with reduced (or no) chemotherapy. Patients were randomized to 4 to 6 cycles of ABVD alone compared to subtotal nodal irradiation (STNI) with or without 2 cycles of ABVD, depending on favorable-risk factors. With an 11-year median follow-up, there was a trend toward improved

Table 1 Select studies of early-stage Hodgkin lymphoma comparing chemoradiation and chemotherapy alone.

Study (accrual years)	Cohort	Evaluable patients	Chemotherapy	Radiation	EFS or FFS (%)	OS (%)
NCIC-ECOG HD6 (Meyer et al. 2005, 2012) (1994–2002)	Non-bulky, IA–IIA	203	None (for low risk) or ABVD×2	STNI 35 Gy	80 (12y)[a]	87 (12y)[b]
		196	ABVD×4–6	None	85	94
EORTC-GELA H9-F, interim analysis (Thomas et al. 2007) (1997–2004)	Early favorable I–II, with CR to initial chemotherapy	239	EBVP×6	IFRT 36 Gy	89 (4y)[c]	98 (4y)[d]
		209	EBVP×6	IFRT 20 Gy	85	100
		130	EBVP×6	None	69	97
MSKCC 90–44 (Straus et al. 2004) (1990–2000)	Non-bulky I–II, or non-bulky IIIA	76	ABVD×6	IFRT or modified EFRT 36 Gy	–	97 (5y)[e]
		76	ABVD×6	None	–	90

Adapted from Kasamon (2009)
NCIC-ECOG National Cancer Institute of Canada–Eastern Cooperative Oncology Group, *EORTC-GELA* European Organization for Research and Treatment of Cancer–Groupe d'Etude des Lymphomes de l'Adulte, *MSKCC* Memorial Sloan Kettering Cancer Center, *CR* complete remission, *ABVD* doxorubicin, bleomycin, vinblastine, and dacarbazine, *EBVP* epirubicin, bleomycin, vinblastine, and prednisone, *STNI* subtotal nodal irradiation, *IFRT* involved-field radiation therapy, *EFRT* extended-field radiation therapy, *EFS* event-free survival, *FFS* failure-free survival, *OS* overall survival
[a] $P=0.6$
[b] $P=0.04$
[c] $P<0.001$ (36 Gy vs. 20 Gy vs. no RT); $P=0.19$ (36 Gy vs. 20 Gy)
[d] $P=0.41$
[e] $P=0.08$

12-year freedom from progression (FFP) ($P=0.05$) but inferior OS ($P=0.04$) in the RT arm as compared to the no-RT arm (Meyer et al. 2012) (Table 1). In the subgroup of patients with poorer-risk disease, there was significantly improved disease control but inferior OS in patients treated with RT compared to chemotherapy alone. In patients with favorable-risk features, there was no difference in disease control or OS between the two arms. Inferior OS in the RT arm was attributed to deaths from causes other than lymphoma or early toxicity. Of the 33 secondary malignancies reported in this trial, 23 were in the RT arm. It is crucial to note that the HD6 trial utilized much more extensive, nearly antiquated RT than would typically be delivered today. The routine use of STNI has long been abandoned, particularly in the patient population studied in this trial. STNI is associated with well-known risks of late side effects that accompany extensive RT volumes treated to relatively high doses. Thus, this trial does not give us insight into the comparison of chemotherapy alone versus chemoradiation using modern HL radiation techniques, fields, and doses. Importantly, in a separate analysis of treatment failures from the study, there was an increased failure rate within the expected extended-field RT (EFRT) field in the chemotherapy-alone arm compared to the RT arm (20/23 vs. 3/10; $P=0.002$) and within what would have been an involved-field RT (IFRT) field (16/23 vs. 2/10; $P=0.02$) (Macdonald et al. 2007). These results highlight the predictable pattern of relapse in patients treated with chemotherapy alone. The trial also reported that in patients treated with ABVD alone, the 5-year FFP was significantly better in those who had achieved a complete remission (CR) after 2 cycles of ABVD (95 % vs. 81 % in those who did not achieve a CR or unconfirmed CR; $P=0.007$) (Meyer et al. 2005). This finding suggests that consolidative RT may be most beneficial in the subset of patients who do not demonstrate an early response to chemotherapy.

The European Organization for Research and Treatment of Cancer (EORTC)–Group d'Etude des Lymphomes d'Adulte (GELA) H9-F trial studied early, favorable HL and investigated the reduction or omission of IFRT for patients who achieved CR following 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) chemotherapy (Thomas et al. 2007). The no-RT arm was closed early due to excess relapses, and with a median follow-up of 5 years, the estimated 4-year failure-free survival (FFS) on interim analysis was only 69 % with EBVP alone (compared to 89 % and 85 % for patients treated with EBVP with 36 and 20 Gy IFRT, respectively) despite patients achieving CR. There was no significant difference in FFS seen between 20 and 36 Gy of radiation, and no difference in OS was noted between any of the arms (Table 1). The results suggest that omission of RT following CR to EBVP leads to unacceptable failure rates but that RT dose can be reduced to 20 Gy; however, some researchers suggest that excess treatment failures may be related to ineffective chemotherapy.

A randomized study conducted at the Memorial Sloan Kettering Cancer Center compared 6 cycles of ABVD with or without RT for non-bulky, mostly limited-stage disease (Straus et al. 2004). No significant difference in 5-year FFP was observed (86 % chemoradiation vs. 81 % ABVD alone, $P = 0.61$), although the study had significant limitations in that it was powered to detect a 20 % difference. There was a trend toward better 5-year OS in the RT arm (97 % vs. 90 %; $P = 0.08$) (Table 1), although longer follow-up would be required to capture the impact of late effects.

In an early randomized study investigating "modern" chemotherapy in all stages of HL, a study from the Tata Memorial Hospital (Mumbai, India) randomized patients achieving a CR to 6 cycles of ABVD chemotherapy to additional consolidation RT versus no further therapy and demonstrated a survival benefit with RT (Laskar et al. 2004). Eight-year event-free survival (EFS) and OS in the chemotherapy-alone arm were 76 % and 89 %, respectively, compared to 88 % and 100 % in the combined modality arm ($P = 0.01$; $P = 0.002$). Unfortunately, this study had some limitations, including short follow-up period and heterogeneity in stage, disease bulk (15 % bulky), mediastinal involvement (72 % uninvolved), age (46 % under age 15 years), and histology (11 % lymphocyte-predominant and mostly mixed cellularity). When evaluating response based on disease stage, patients with advanced-stage (III/IV) disease demonstrated better EFS and OS with consolidation RT, whereas those with stage I–II disease had similar outcomes between the two arms.

It should be emphasized that, aside from the Tata Memorial Hospital study, patients with bulky disease were excluded from these randomized studies of chemotherapy alone. Although combined modality therapy remains the standard for patients with bulky, limited-stage HL, the role and necessity of modern RT in this subgroup have not been adequately evaluated. In a randomized study by Aviles et al., patients with bulky early-stage HL were randomized to 6 cycles of ABVD, a combined modality arm involving ABVD with RT, or EFRT alone (Aviles and Delgado 1998). After a median follow-up duration of 11.4 years, significantly greater tumor control and OS were seen with combined modality therapy. Patients in the combined modality arm had a 12-year OS of 88 %, compared to 53 % in patients who received RT alone and 59 % who received chemotherapy alone ($P < 0.01$).

In a meta-analysis of un-confounded trials of combined modality therapy compared to chemotherapy alone for early-stage HL, the impact of RT was assessed among five randomized controlled studies in which the only difference in the arms was the use of RT (Herbst et al. 2011). The studies included were Mexico B2H031, a study of 201 patients treated with 6 cycles of ABVD ± RT (Aviles et al. discussed above); Cancer and Leukemia Group B (CALGB) 7751, a study of 37 patients treated with 6 cycles of cyclophosphamide, vinblastine, procarbazine, and prednisone (CVPP) ± RT; EORTC-GELA H9-F, a study of 568 patients treated with 6 cycles of EBVP ± RT (20 and 36 Gy) (discussed above); Argentine Group for Acute Leukemia Treatment (GATLA) 9-H-77, a study of 277 patients treated with 6 cycles of CVPP ± RT; and MSKCC 90–44,

a study of 152 patients treated with 6 cycles of ABVD ± RT (discussed above). In total, 1,245 patients made up the cohort, and the meta-analysis demonstrated an improvement in both tumor control (hazard ratio [HR], 0.41; 95 % confidence interval [CI], 0.25–0.66) and in OS (HR, 0.4; 95 % CI, 0.27–0.61) with the addition of RT to chemotherapy versus chemotherapy alone. However, a weakness of this meta-analysis was the limited follow-up averaging 60 months.

A recently published population-based retrospective study using the National Cancer Data Base evaluated outcomes of over 9,000 patients with early-stage HL treated with combined modality therapy or chemotherapy alone (Olszewski et al. 2015). Combined modality therapy was associated with better OS (HR, 0.61; 95 % CI, 0.53–0.70) compared to chemotherapy alone. However, similar to the above meta-analysis, follow-up was limited (median, 6.1 years).

2.1.2 Advanced-Stage Hodgkin Lymphoma

In advanced-stage HL, the role of RT is less defined (Aleman et al. 2003; Fabian et al. 1994; Johnson et al. 2010; Loeffler et al. 1998), and studies have variably supported and refuted the integration of RT into treatment regimens. For example, a prospective, non-randomized study as part of the larger UKLG LY09 trial evaluated the effect of consolidative RT in patients with advanced-stage HL who received 6–8 cycles of chemotherapy. Patients were referred for IFRT for incomplete response to chemotherapy or bulk disease at presentation. The study suggested both a PFS and OS advantage with consolidative RT for advanced HL, despite the presence of more adverse prognostic features in the irradiated patients (Johnson et al. 2010). A meta-analysis investigating the addition of RT to chemotherapy in patients with primarily stage III/IV disease demonstrated an improvement in tumor control rate of 11 % at 10 years (95 % CI, 4–18 %) with the addition of RT. Yet there was no benefit in OS with the addition of RT ($P = 0.6$) (Loeffler et al. 1998). Given the more advanced disease in this second study and the use of larger RT fields (total nodal irradiation [TNI] and EFRT), it has been hypothesized that in patients with advanced-stage disease, the benefit in PFS from RT may be limited due to late RT toxicities, specifically cardiovascular and secondary malignancies. Thus, the use of RT in patients with advanced disease might be limited to those who present with one or two sites of bulky disease. It is crucial to point out that those patients undergoing Stanford V treatment for stage III/IV disease are required to receive RT to sites of initial bulky disease.

2.2 Patient Risk Stratification and Response-Based Therapy

With a primary goal of minimizing unnecessary treatments and toxicity, the question arises: what is the best way to identify patients who will benefit most from RT? The use of interim ^{18}F-FDG positron emission tomography (PET) to stratify patients based on early response to treatment is the subject of several ongoing trials and may help elucidate which patients may derive the most benefit from addition of RT to chemotherapy (Table 2). It has been repeatedly recognized that the results of ^{18}F-FDG PET, when performed after only 2 or 3 cycles of chemotherapy, are prognostically significant in classical HL whether in the frontline (Friedberg et al. 2004; Furth et al. 2009; Gallamini et al. 2007, 2014; Hutchings et al. 2006; Straus et al. 2011) or relapsed (Devillier et al. 2012; Jabbour et al. 2007; Moskowitz et al. 2010) setting. A negative mid-treatment PET scan has been associated with favorable outcomes, while a positive mid-treatment PET scan generally portends worse outcomes, although results have been quite variable due in part to the small number of PET-positive patients represented in these series. Recently, clinical trials have used end-of-chemotherapy PET to guide whether and which sites to irradiate. For example, PET performed after completion of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) has been used to restrict RT to residual FDG-avid masses in the German Hodgkin Study Group (GHSG)

Table 2 Selected studies employing interim PET to guide radiation treatment in early-stage Hodgkin lymphoma

Study	Characteristics	Timing of interim PET	Treatment
UK NCRI RAPID trial (Radford et al. 2015)	Stage IA or IIA, non-bulky disease	After ABVD × 3	PET–, randomize to IFRT (30 Gy) vs. no further therapy
			PET+, further ABVD + IFRT (30 Gy)
GHSG HD16 (ClinicalTrials.gov 2016a)	Stage I–II, favorable disease	After ABVD × 2	Standard arm: IFRT (20 Gy) regardless of interim PET
			Experimental: PET–, no further therapy
			Experimental: PET+, IFRT (20 Gy)
EORTC-GELA H10 (Raemaekers et al. 2014; ClinicalTrials.gov 2014)	Stage I–II, favorable and unfavorable, including bulky disease	After ABVD × 2	Standard arm: complete ABVD + INRT (30 Gy) regardless of interim PET
			[Experimental: PET–, complete ABVD without RT] (arm closed after interim analysis)
			Experimental: PET–, complete ABVD + INRT (30 Gy) (new arm since interim analysis)
			Experimental: PET+, BEACOPPesc + INRT (30 Gy)

UK NCRI UK National Cancer Research Institute, *GHSG* German Hodgkin Study Group, *EORTC-GELA* European Organization for Research and Treatment of Cancer–Groupe d'Etude des Lymphomes de l'Adulte, *PET* positron emission tomography, *ABVD* doxorubicin, bleomycin, vinblastine, and dacarbazine, *IFRT* involved-field radiotherapy, *INRT* involved-node radiotherapy, *BEACOPPesc* bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
Adapted from Kasamon (2011), Table 2

HD15 trial, with encouraging outcomes in advanced HL (Engert et al. 2012). In the GHSG HD18 trial for advanced HL, patients achieving a negative PET after 2 cycles of escalated BEACOPP do not receive RT (ClinicalTrials.gov 2015).

In early HL, several large, randomized clinical trials, including the UK National Cancer Research Institute (NCRI) RAPID, EORTC-GELA H10, and GHSG HD16 trials, are evaluating response-based determination of therapy based on PET performed after 2 or 3 cycles of first-line chemotherapy (Radford et al. 2015; Raemaekers et al. 2014; ClinicalTrials.gov 2014, 2016a) (Table 2). These trials seek to determine when to escalate a patient's therapy and when to omit RT based on a negative interim PET scan. Although this approach may be valid, caution is advised, as it is not yet clear whether the excellent cure rates already achievable in such patients will be maintained with de-escalation of therapy. Indeed, in the EORTC-GELA H10 trial for patients with early favorable or unfavorable HL, the experimental arm in which patients with negative PET after 2 cycles of ABVD receive 1 or 2 additional cycles of ABVD without RT was closed early due to excess treatment failure (9 events vs. 1 event with RT in the favorable subgroup; 16 events vs. 7 events with RT in the unfavorable subgroup) (Raemaekers et al. 2014). RT has since been added to this arm following completion of ABVD. The recently published UK NCRI RAPID trial, which randomized early-stage HL patients with negative PET following 3 cycles of ABVD to IFRT versus no further treatment, failed to demonstrated noninferiority of the observation arm, with slightly worse 3-year PFS (90.8 % in the observation group vs. 94.6 % in the RT group, $P = 0.16$ per intention-to-treat analysis) (Radford et al. 2015). However, given excellent 3-year OS outcomes for both groups (97.1 % in the RT group and 99.0 % in the observation group, $P = 0.27$) and that most patients with negative PET did well without addition of RT, this trial suggests that it may be reasonable to consider omitting RT with negative PET following 3

cycles of ABVD on an individual basis, although the short follow-up is important to consider.

In the pediatrics population, interim PET is being actively used to guide therapy. In the recently completed Children's Oncology Group (COG) AHOD 0031 study, patients received 2 cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) followed by response assessment, and patients with rapid early response (RER) based on computed tomography (CT) criteria received 2 additional cycles of ABVE-PC followed by a second response assessment (Friedman et al. 2014). Those with a CR (meeting both PET and CT criteria) were randomized to 21 Gy IFRT or no further therapy. Patients with a RER who did not have a CR were all assigned to receive IFRT. Slow early responders (SER) were all randomized to either 2 additional cycles of ABVE-PC or dexamethasone, etoposide, cisplatin, and cytarabine (DECA) followed by an additional 2 cycles of ABVE-PC. All SER patients received 21 Gy IFRT after chemotherapy. Four-year EFS rates were 86.9 % for RER patients versus 77.4 % for SER patients ($p < 0.001$). The 4-year OS rate for RER patients was 98.5 % versus 95.3 % for SER patients ($p < 0.001$). The 4-year EFS rate was 87.9 % for RER/CR patients randomized to receive IFRT versus 84.3 % for those randomized to no IFRT ($P = 0.11$). These results suggest that early response to chemotherapy defined by early reduction (60 %) in tumor size on CT after 2 cycles can be a powerful predictor of outcome and help optimize subsequent treatment. A secondary analysis of PET response after 2 cycles of ABVE-PC demonstrated that PET may further assist with treatment optimization.

Because the role of interim PET in guiding lymphoma treatment is still under investigation, treatment decisions on this basis in the adult setting are best made in the context of clinical trials. Furthermore, the limitations of PET scanning must be considered, including the risk of false positive and false negatives, uncertainty with regard to the definition of an adequate metabolic response, and issues with the reproducibility and interpretation of a scan.

2.3 Radiation Field Size

EFRT, which delivers RT to both involved and uninvolved lymph node regions, is now rarely used for HL. The effectiveness of chemotherapy to address microscopic disease has permitted reduction in the radiation delivered both in terms of field size and dose, without compromise of outcome (Bonadonna et al. 2004; Ferme et al. 2007) (Fig. 1). IFRT, in which the RT field is limited to the clinically involved lymph node group or groups, became the standard of care in the context of combined modality therapy (Yahalom and Mauch 2002). Multiple trials, including the EORTC-GELA H8U trial and GHSG HD8 study, have demonstrated no difference in disease

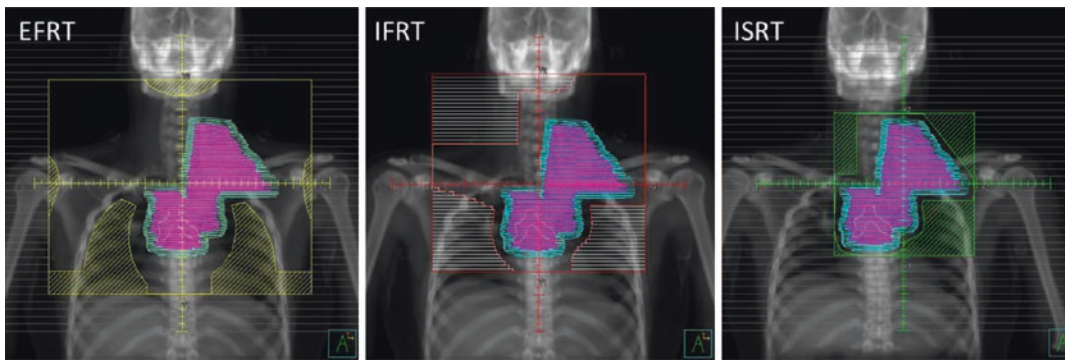

Fig. 1 Mantle field (extended-field radiotherapy, *EFRT*) is represented by the *yellow* field, involved-field radiotherapy (*IFRT*) by the *red* field, and involved-site radiotherapy (*ISRT*) by the *green* field. Clinical target volume and planning target volume (with 1 cm margin) are represented by the *pink* and *blue* volumes, respectively

control outcomes between IFRT and more extensive RT fields (Ferme et al. 2007; Engert et al. 2003). At the same time, EFRT has been associated with increased toxicity and risk of secondary cancers compared with IFRT (Franklin et al. 2006; Klimm et al. 2007).

Patients with early-stage HL treated with chemotherapy alone have an elevated risk for relapse in the initially involved lymph nodes (Macdonald et al. 2007; Shahidi et al. 2006; Canellos et al. 2010). Given the desire to reduce treatment field size, the EORTC-GELA recently introduced the concept of involved-node radiotherapy (INRT), which includes treatment of only the initially involved macroscopic disease. For INRT, it is essential to use all available clinical information, including pre- and post-chemotherapy imaging with CT and ^{18}F-FDG PET scan to define the treatment field according to the original extent of disease. Per EORTC-GELA guidelines, the clinical target volume should include only the site of originally involved lymph nodes identified prior to chemotherapy (Girinsky et al. 2006, 2008). In a study of early-stage HL, 36 % of patients had suspicious lymph nodes on ^{18}F-FDG PET that were occult on CT (Girinsky et al. 2007). Similarly, in patients with early-stage HL enrolled in the randomized EORTC-GELA H10 trial, ^{18}F-FDG PET identified at least 1 additional FDG-avid lymph node in 70 % of patients and 1 additional lymph node area in 41 % of patients compared to CT alone (Girinsky et al. 2014). Therefore, when using an INRT approach, pre-chemotherapy evaluation with PET is required to help delineate the extent of disease. Controversy exists regarding the appropriate design of INRT fields and the optimal margins to be used, with North American and European groups using different definitions and guidelines (Girinsky et al. 2006, 2008; Campbell et al. 2008; Eich et al. 2008). Therefore, it is important to delineate the INRT field according to the specific protocol being followed.

Studies demonstrating the feasibility of INRT are still limited with short follow-up and small numbers, although early clinical data are emerging. Two retrospective studies of HL patients who received INRT per EORTC-GELA guidelines demonstrated excellent disease control with minimal toxicity, with 4 relapses (2 in-field) in 50 patients in Paumier et al. and 3 relapses (2 in-field) in 97 patients in Maraldo et al., both studies with a median follow-up of approximately 50 months (Paumier et al. 2011; Maraldo et al. 2013). The EORTC-GELA is now investigating INRT in early favorable and early unfavorable HL in the H10 trial (ClinicalTrials.gov 2014). Providing further insight into the potential role for reduced treatment field size, Campbell et al. analyzed the outcomes of 325 patients with limited-stage HL treated with combined modality therapy from 1989 to 2005 (Campbell et al. 2008). EFRT was used until 1996 (39 % of patients), IFRT between 1996 and 2001 (30 % of patients), and INRT from 2001 onward (31 % of patients). It is important to note that the INRT fields used in this study were designed with more generous margins (up to 5 cm) as compared to those defined by the EORTC-GELA and GHSG (Girinsky et al. 2006, 2008; Eich et al. 2008), as CT planning was not utilized uniformly, and pre- and post-chemotherapy PET scans were not used. Ninety-five percent of patients received two cycles of chemotherapy. After a median follow-up of 80 months, 12 relapses were identified: 4 after EFRT (3 %), 5 after IFRT (5 %), and 3 after INRT (3 %) ($P = 0.9$). Although no marginal recurrences were identified in patients who underwent INRT, the margins for INRT used in this study were tantamount to a reduced IFRT field.

Building on the concept of INRT, involved-site radiation therapy (ISRT) was recently introduced as part of the recent International Lymphoma Radiation Oncology Group (ILROG) guidelines for modern RT techniques for HL (Specht et al. 2014). In both INRT and ISRT, the pre-chemotherapy gross tumor volume (GTV) determines the clinical target volume (CTV), resulting in significantly smaller irradiated volumes than with IFRT. However, INRT requires pre-chemotherapy imaging (ideally PET-CT) in the treatment position, which is not always available to the radiation oncologist. ISRT accommodates cases in which optimal pre-chemotherapy imaging is not available, and clinical judgment in conjunction with the best available imaging is

used to contour a larger CTV that accounts for the uncertainties in defining the pre-chemotherapy GTV. However, interpretation of ISRT guidelines is variable among expert radiation oncologists (Hoppe and Hoppe 2015), and thus further guidance is needed for effective and consistent implementation of ISRT.

2.4 Radiation Dose

Treatment with combined modality therapy has enabled a reduction in radiation field size and radiation dose compared to the era when radiation treatment was used alone for HL. Lower radiation dose delivered to the target results in lower dose delivered to in-field non-targeted normal tissue. Therefore, reduced toxicity would be expected with modern radiotherapy techniques. The GHSG HD10 study for patients with favorable-risk stage I/II HL demonstrated that, in conjunction with 2 or 4 cycles of ABVD, IFRT delivered to 20 Gy was equivalent to 30 Gy, with no significant differences in rates of freedom from treatment failure and OS (Engert et al. 2010). Additionally, severe acute toxicity (grade 3 or 4) and number of adverse events were greater in patients who received 30 Gy compared to 20 Gy. Unfavorable-risk stage I/II patients were evaluated in the GHSG HD11 study, which was a four-arm study comparing two radiation dose levels (20 Gy vs. 30 Gy) and two chemotherapy regimens (4 cycles of ABVD versus BEACOPP) (Eich et al. 2010). Similar rates of freedom from treatment failure, OS, and PFS were observed with 20 Gy versus 30 Gy IFRT in patients receiving BEACOPP chemotherapy. However, inferiority of 20 Gy compared to 30 Gy could not be excluded after 4 cycles of ABVD. Thus, radiation dose is contingent upon the chemotherapy regimen used, and 30 Gy IFRT is still recommended following ABVD chemotherapy for patients with unfavorable-risk disease. The grade 3–4 toxicity rate was reduced with the lower dose of RT, from 12 to 5.7 %.

The data informing us on the potential for radiation late effects are largely based on studies in which patients who received RT were young and received radiation doses and fields sufficient for cure without the use of chemotherapy. Thus, the radiation fields in these studies were overall more extensive and the radiation doses higher than typically used in combined modality regimens in the modern era. Secondary malignancy and cardiovascular disease are the two most commonly reported late effects that have a significant impact on longevity and quality of life in survivors (Ng et al. 2002). The most common secondary malignancies in HL survivors include lung cancer, breast cancer (for women), gastrointestinal cancer, and thyroid cancer (Ng et al. 2002; Hodgson et al. 2007; Dores et al. 2002). Over the last decade, several studies have attempted to quantify the risk for developing cancer based on the radiation dose and the use of chemotherapy, specifically with nested case–control studies of HL survivors who developed or did not develop the second malignancy of interest. In a study evaluating the risk of breast cancer, Travis et al. demonstrated that radiation doses to the breast of 4 Gy or more were associated with an increased risk of subsequent breast cancer compared to patients who had not received RT (Travis et al. 2003). A separate study evaluating the risk of secondary lung cancer reported an increased risk with radiation doses to the lung of 5 Gy or more (Travis et al. 2002). With regard to the risk of developing coronary heart disease (CHD), a recent study demonstrated a linear dose–response relationship between risk of CHD and increasing mean heart dose, with an excess relative risk per Gy of 7.4 % and a 2.5-fold increased risk of CHD for patients receiving a mean heart dose of 20 Gy compared with patients not treated with mediastinal RT (van Nimwegen et al. 2016).

Multiple studies have now suggested that a lower RT dose should translate into a reduction in late effects when used judiciously (Travis et al. 2002, 2003, 2006; van Nimwegen et al. 2016; van Leeuwen et al. 2003; Arakelyan et al. 2010). It has also been demonstrated that a reduction in the volume of normal tissue treated can translate into a reduction in late effects (De Bruin et al. 2009). This finding is particularly important since the majority of late effects data is derived from studies of EFRT alone as the primary curative treatment for HL. It is therefore to be

expected that the risks of these serious late radiation-related toxicities could be significantly decreased by reducing the radiation dose to non-targeted critical structures, such as the heart, thyroid, breasts, and lung.

2.5 Advanced Radiation Therapy Techniques

Intensity-modulated radiation therapy (IMRT) is a sophisticated radiotherapy technique that employs multiple radiation beams aimed at a target from different directions, with the beams varying in size, shape, and intensity that create a 3D dose distribution conforming to the target volume. IMRT succeeds in increasing dose conformality to the actual target volume compared to simpler, conventional RT techniques that were historically used in the treatment of HL. However, the dose is "spread out" with the use of IMRT such that a larger volume receives a low dose compared to conventional techniques. Several studies have been published comparing the dose distributions of conventional 3D conformal RT (3DCRT) plans with IMRT in patients with HL. In an initial study, investigators compared IMRT with 3DCRT and demonstrated a reduction in mean lung dose by 12 % with IMRT (Goodman et al. 2005). However, Weber et al. reported that in a nonlinear model for development of secondary malignancies, IMRT increased the risk of breast, lung, and thyroid cancers compared with 3DCRT as a result of increased volume of normal tissue receiving low doses of RT (Weber et al. 2011). Similarly, a recent study from the GHSG demonstrated reduced dose to the heart and spinal cord but increased dose to the lung and breasts with the use of IMRT compared to 3DCRT (Koeck et al. 2012).

Clinical studies using modern radiation techniques are only beginning to emerge. Paumier et al. reported on 32 patients treated to an INRT field with IMRT following chemotherapy and demonstrated 5-year PFS and OS of 91 % and 95 %, respectively, comparable to standard techniques (Paumier et al. 2011). Only 1 patient developed an in-field relapse, and only 1 patient developed grade 3 pneumonitis. Filippi et al. reported similarly good outcomes in early-stage HL patients treated to an ISRT field with IMRT following chemotherapy, with 1 out-of-field relapse out of 41 patients (median, 2-year follow-up), 100 % relapse-free survival, and no grade 3 acute toxicity (Filippi et al. 2014).

Unlike X-rays, protons (PT) are charged particles with mass and travel a finite distance. The actual range of protons in tissue can be controlled, thereby eliminating the "exit" dose to non-targeted tissues (Fig. 2). In addition, protons deposit most of their radiation dose in tissue near the end of their range in a striking pattern called the Bragg peak, with relatively little dose deposited along the "entrance" path. Dosimetric studies evaluating the use of PT in HL date back to 1974 (Archambeau et al. 1974); however, more sophisticated treatment planning studies have since been published. In a prospective phase II study from the University of Florida (Jacksonville, FL; UF) of INRT in patients with mediastinal HL (Hoppe et al. 2012), the first 10 patients enrolled underwent treatment planning with 3DCRT (AP/PA), IMRT, and PT techniques and were offered treatment with the plan that best spared the organs at risk while maintaining appropriate target coverage. In all 10 cases, PT was associated with the best plan, and all patients were offered treatment with PT. Specifically, the mean dose to the heart was 19.4 Gy with 3DCRT, 12.2 Gy with IMRT, and 8.9 cobalt Gy equivalent (CGE) with PT. The mean lung dose was 13.2 Gy for 3DCRT, 10.6 Gy for IMRT, and 7.1 CGE for PT. In a study from the MD Anderson Cancer Center (Houston, TX), 10 patients were treated with PT for mediastinal lymphoma, and when comparing PT versus conventional photon therapy (3DCRT) plans for these patients, PT reduced the mean heart dose (8.8 Gy vs. 17.7 Gy) and mean lung dose (6.2 Gy vs. 9.5 Gy) (Li et al. 2011). Due to the tissue density in the lung, however, the dose may be underestimated for the PT plans.

While clinical studies involving PT are still underway, early results from the UF phase II study introduced above have recently been published (Hoppe et al. 2014). Involved-node proton therapy (INPT) was used as a component of combined modality therapy for patients with stage I–III HL with mediastinal involvement. Five

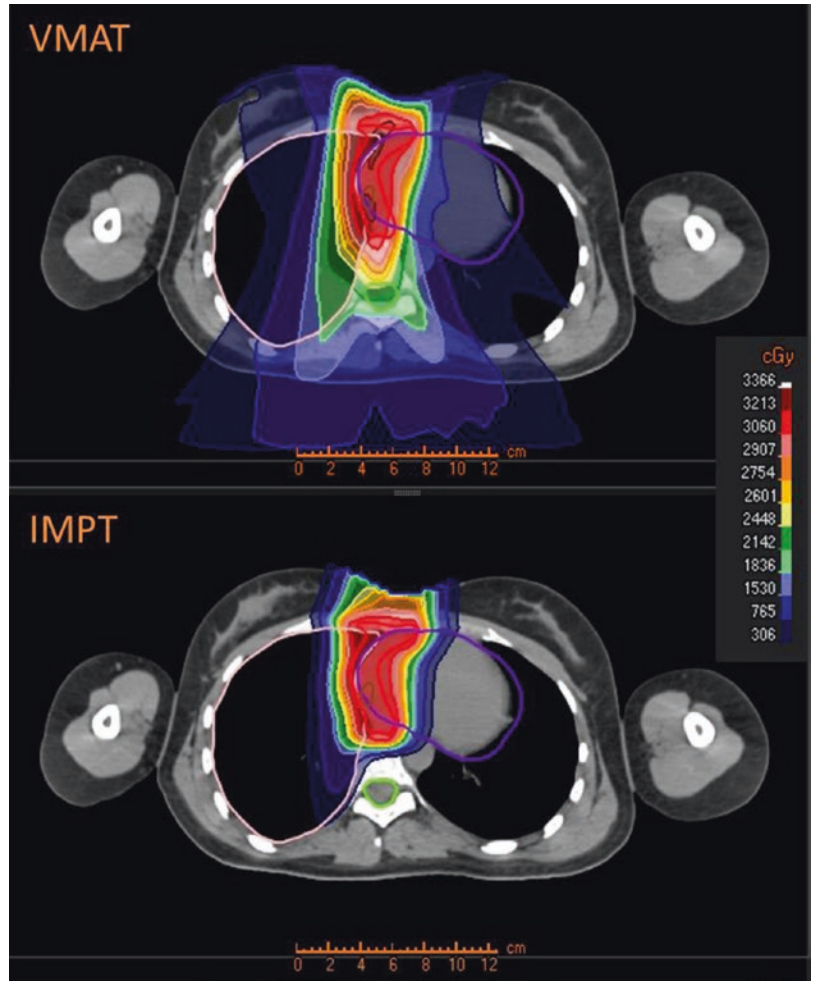

Fig. 2 Comparison of volumetric-modulated arc therapy (*VMAT*) vs. intensity-modulated proton therapy (*IMPT*) plans demonstrating representative differences in dose distributions with each technique (Courtesy of Dr. Matthew Ladra, Provision Center for Proton Therapy)

children received 15–25.5 CGE of INPT following 4 cycles of chemotherapy (primarily ABVE-PC), and 10 adults received 30.6–39.6 CGE of INPT following 3–6 cycles of ABVD chemotherapy. With a median follow-up of 37 months, one patient had relapse both inside and outside the treatment field, and the 3-year relapse-free survival and event-free survival were 93 % and 87 %, respectively, similar to the outcomes with conventional photon therapy. There were no acute or late grade 3 non-hematologic toxicities.

PT treatment planning is more complex than X-ray treatment planning. The depth that protons will travel in tissue depends on their energy and the composition of tissue traveled through. Minor variations in daily patient positioning may result in variations in the proton path length that must be accounted for in the treatment planning process. Improved treatment planning and delivery systems will reduce this uncertainty and minimize adjustments necessary in the treatment planning process. Clinical experience with current follow-up has not demonstrated an increase in the risk of second malignancy with PT despite concerns regarding secondary neutron scatter (Chung et al. 2013).

3 Non-Hodgkin Lymphoma

Similar to HL, radiation therapy was the only effective treatment for NHL until the introduction of effective chemotherapies starting in the

1960s. Since then, the treatment paradigm has shifted toward combined modality therapy with RT and chemoimmunotherapy, although indications for combination therapy versus monotherapy or even observation in select cases remain inconsistent.

3.1 Role of Radiation Therapy

3.1.1 Limited-Stage Non-Hodgkin Lymphoma

The role of RT in limited-stage diffuse large B-cell lymphoma (DLBCL), the most common form of NHL, remains controversial despite multiple randomized trials undertaken in the 1980s and 1990s (Table 3). By the 1980s, two approaches were widely utilized to treat localized intermediate- and high-grade NHL: doxorubicin-containing chemotherapy alone for 6–8 cycles or a shorter course (typically 3 cycles) of chemotherapy followed by IFRT. The presumed advantages of longer-course chemotherapy are avoidance of long-term complications of RT, along with higher overall doses of systemic therapy to address microscopic disease, while the possible advantages of short-course chemotherapy with RT are decreased risk of cardiac toxicity and direct local therapy to detectable disease with RT.

The Southwest Oncology Group (SWOG) evaluated these two approaches in SWOG 8736, which compared 8 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy with shorter course CHOP chemotherapy (3 cycles) followed by consolidative IFRT for patients with localized, intermediate- or high-grade NHL (non-bulky or bulky stage I, non-bulky stage II disease) (Miller et al. 1998). Short-course chemotherapy with consolidative RT initially demonstrated a benefit in 5-year PFS and OS and fewer cardiac events (OS 82 % vs. 72 %, $P = 0.02$) (Table 3), establishing combined modality treatment as the standard for limited-stage disease. However, these differences did not persist due to late relapses in the RT arm per an update in abstract form (Miller et al. 2001), suggesting a need for additional chemotherapy for higher risk patients.

Around this time, the British Columbia Cancer Agency published results from a long-term, 18-year experience treating patients with limited-stage diffuse large-cell lymphoma with 3 cycles of CHOP (or CHOP-containing) chemotherapy followed by 30 Gy RT (Shenkier et al. 2002). With a median follow-up of nearly 14 years, this treatment regimen was found to be overall effective, with estimated 5- and 10-year PFS of 81 % and 74 %, respectively, and 5- and 10-year OS of 80 % and 63 %, respectively. Patients with a greater number of negative prognostic factors in a modified International Prognostic Index (IPI) had worse PFS, disease-specific survival (DSS), and OS with this treatment. Further, this study confirmed findings from SWOG 8736 that the majority of relapses occurred outside the radiation field, again suggesting the importance of more effective systemic therapy for improved outcomes, especially for higher risk patients.

ECOG 1484 sought to address the question of whether low-dose RT could improve outcomes in patients receiving full-course chemotherapy, by randomizing patients with stage I or II diffuse aggressive lymphoma who had CR after 8 cycles of CHOP chemotherapy to 30 Gy RT versus observation (Horning et al. 2004). Patients with partial response (PR) to chemotherapy all received 40 Gy RT. Despite a higher percent of patients with bulky disease in the RT arm, the addition of low-dose RT in patients with CR improved disease-free survival (DFS) (73 % vs. 56 % for CHOP alone, $P = 0.05$) and local control, with a trend (although not statistically significant) toward better overall survival (Table 3). A majority of patients with PR to CHOP chemotherapy were event-free at 6 years following consolidative RT, although conversion to CR did not significantly influence relapse rates or survival outcomes.

To test the efficacy of highly intensive chemotherapy-alone versus combined modality treatment in younger patients, the GELA in the LNH 93–1 study randomized patients under 61 years of age with localized aggressive lymphoma to 3 cycles of CHOP chemotherapy followed by IFRT versus chemotherapy alone with

Table 3 Select studies of localized non-Hodgkin lymphoma comparing chemoradiation and chemotherapy alone

Study (accrual years)	Cohort	Evaluable patients	Chemotherapy	Radiation	PFS, DFS, or EFS (%)	OS (%)
SWOG 8736 (Miller et al. 1998) (1988–1995)	Stage I (including bulky) and II (non-bulky), intermediate- and high-grade histology	201	CHOP×8	None	64 (5y)[a]	72 (5y)[b]
		200	CHOP×3	IFRT 40–55 Gy	77	82
ECOG 1484 (Horning et al. 2004) (1984–1992)	Stage I–II (I with risk factors: mediastinal or retroperitoneal involvement, bulky disease), aggressive histology	93 (CR)	CHOP×8	None	56 (6y)[c]	71 (6y)[d]
		79 (CR)	CHOP×8	IFRT 30 Gy	73	82
		71 (PR)	CHOP×8	IFRT 40 Gy	63	69
GELA LNH 93–1 (Reyes et al. 2005) (1993–2000)	Stage I–II (including bulky), aggressive histology, age <61, IPI=0	318	ACVBP×3+ consolidation	None	82 (5y)[e]	90 (5y)[f]
		329	CHOP×3	IFRT 40 Gy	74	81
GELA LNH 93–4 (Bonnet et al. 2007) (1993–2002)	Stage I–II (including bulky), aggressive histology, age >60, IPI=0	277	CHOP×4	None	61 (5y)[g]	72 (5y)[h]
		299	CHOP×4	IFRT 40 Gy	64	68

SWOG Southwest Oncology Group, *ECOG* Eastern Cooperative Oncology Group, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *IPI* International Prognostic Index, *CR* complete remission, *PR* partial response, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *ACVBP* doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; *IFRT* involved-field radiation therapy, *PFS* progression-free survival, *DFS* disease-free survival, *EFS* event-free survival, *OS* overall survival

[a] $P=0.03$
[b] $P=0.02$
[c] $P=0.05$
[d] $P=0.24$
[e] $P<0.001$
[f] $P=0.001$
[g] $P=0.6$
[h] $P=0.5$

dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) (Reyes et al. 2005). With a median follow-up of 7.7 years, patients receiving ACVBP chemotherapy alone had higher 5-year EFS (82 % vs. 74 % for CHOP + IFRT, $p<0.001$) and overall survival (90 % vs. 81 % for CHOP + IFRT, $P=0.001$) (Table 3). The difference remained significant in separate analyses of both subgroups with and without bulky disease. However, acute toxicity was significantly higher in patients receiving ACVBP chemotherapy versus CHOP-based combined modality therapy, with grade 3–4 infection in 12 % versus 1 % of patients. The patients treated with combined modality treatment did have fewer initial site relapses (23 % vs. 41 % for chemotherapy alone), with most relapses occurring outside the radiation field.

Another GELA study, LNH 93–4, sought to evaluate the role of radiation therapy in the treatment of elderly patients with localized stage I or II aggressive lymphoma (Bonnet et al. 2007). Patients older than 60 years with no adverse prognostic factors in the IPI were randomized to 4 cycles of CHOP with or without consolidative IFRT. With a median follow-up of 7 years, there were no differences in 5-year estimates of EFS (61 % for CHOP alone vs. 64 % for CHOP + IFRT) or OS (72 % for CHOP alone vs. 68 % for CHOP + IFRT) (Table 3). Despite patients with fewer risk factors in this trial, EFS

was lower than in the other trials, and other concerns include outdated radiation fields and techniques and heterogeneity of patient characteristics and treatments.

These five studies—four prospective, randomized trials and one long-term, large retrospective study—have not established a consensus standard of care but instead have been interpreted differently by medical and radiation oncologists. The lack of long-term survival benefit and concerns of secondary malignancy have been used to refute the role of RT and support a chemotherapy-only regimen (Sehn 2012). However, the studies also unquestionably demonstrate a local control benefit with RT and systemic relapses as the major cause of treatment failure. We can conclude from these studies that there is a need for better systemic therapy and that RT cannot replace inadequate chemotherapy.

The recent introduction of the anti-CD20 antibody, rituximab, has significantly improved systemic outcomes for DLBCL (Coiffier et al. 2010; Feugier et al. 2005; Habermann et al. 2006; Pfreundschuh et al. 2006, 2008). A phase II study combining rituximab-CHOP (R-CHOP) with consolidative RT for limited-stage DLBCL, SWOG 0014, demonstrated higher PFS and OS compared to SWOG 8736 (discussed above) without rituximab (Persky et al. 2008). At the same time, RT techniques have also been evolving toward more conformal therapy. As the previous studies were carried out in the pre-rituximab, pre-conformal RT era, we await randomized studies for DLBCL including these newer treatments. For now, we turn to the results of a larger retrospective analysis and information from related randomized studies to guide management decisions.

What is the role of consolidative RT for patients with DLBCL treated with R-CHOP systemic therapy? A retrospective study from MD Anderson (Phan et al. 2010) sought to address this question by analyzing outcomes of patients with DLBCL treated between 2001 and 2007. Of 291 patients with stage I–IV DLBCL who achieved CR with 6–8 cycles of R-CHOP systemic therapy, those who received consolidative IFRT (30–40 Gy) had significantly better 5-year PFS (90 % vs. 75 % for no RT, $p < 0.001$) and OS (91 % vs. 83 % for no RT, $P = 0.015$). A matched-pair analysis of the subgroup of patients with stage I–II DLBCL who received 6–8 cycles of R-CHOP also indicated longer PFS and OS for those receiving RT.

In an amendment to the RICOVER-60 trial by the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL), the role of RT in the rituximab era was evaluated in elderly patients with all stages of DLBCL in a non-randomized, prospective study (Held et al. 2014). When comparing patients with bulky disease treated with 6 cycles of R-CHOP (the best systemic therapy arm from the RICOVER-60 trial) with or without IFRT to initial bulky and extralymphatic disease, the addition of RT correlated with superior EFS (66 % vs. 40 %, $P = 0.001$) in an intention-to-treat analysis and significantly better 3-year EFS (80 % vs. 54 %, $P = 0.001$), PFS (88 % vs. 62 %, $p < 0.001$), and OS (90 % vs. 65 %, $P = 0.001$) in a per-protocol analysis. In the recently completed UNFOLDER trial, also by the DSHNHL, patients were initially randomized between two R-CHOP schedules and between radiation and observation for patients with extranodal or bulky disease (ClinicalTrials.gov 2016b). The no-RT arms were stopped when interim analysis showed a higher failure rate in those arms. Together, these studies strongly suggest a benefit of consolidative RT in patients with bulky disease in the rituximab era.

3.1.2 Advanced-Stage Non-Hodgkin Lymphoma

Regarding advanced (stage III–IV) DLBCL, the role of RT is not well defined in the absence of randomized trials and remains at the discretion of treating physicians. The current standard is R-CHOP systemic therapy for 6 cycles, with consideration of RT for bulky disease, extranodal involvement, or incomplete response to systemic therapy. As discussed in the previous section of limited-stage DLBCL, a non-randomized amendment to the RICOVER-60 trial by the DSHNHL demonstrated superior EFS, PFS, and OS in elderly patients with all stages of DLBCL with bulky disease when RT was added to 6 cycles of R-CHOP

(per-protocol analysis) (Held et al. 2014). The remainder of available data addressing the role of RT for advanced-stage DLBCL comes from single-institution retrospective studies, as well as a multi-institution retrospective analysis from the National Comprehensive Cancer Network (NCCN). A large retrospective study from MD Anderson of patients with stage I–IV DLBCL (also discussed in the previous section of limited-stage disease) demonstrated that addition of consolidative RT to 6–8 cycles of R-CHOP systemic therapy correlated with better OS and PFS, regardless of stage, in a matched-pair analysis (Phan et al. 2010). Single-institution retrospective studies of patients with stage III–IV DLBCL who achieved a CR to systemic therapy demonstrated improved outcomes (although OS benefit is not always seen) with the addition of consolidation RT to primarily R-CHOP systemic therapy (Shi et al. 2013; Dorth et al. 2012). In a retrospective analysis of 841 patients with all stages of DLBCL treated at NCCN institutions during the rituximab era, Dabaja et al. demonstrated better 5-year OS (91% vs. 83%, $P=0.01$) and FFS (83% vs. 76%, $P=0.05$) in patients receiving RT following R-CHOP versus those who did not (Dabaja et al. 2015b). A matched-pair analysis showed trends for better OS and FFS with addition of RT for patients with stage III/IV disease, but the differences were not statistically significant. Taken together, RT likely improves outcomes for subsets of patients with advanced-stage DLBCL, in particular bulky or extranodal disease; however, randomized, prospective studies are needed to define more clearly those who will derive the most benefit from RT.

3.2 Radiation Dose and Field Size

Regarding RT dose and fields, a retrospective study by Kamath et al. of patients with stage I and II NHL treated with RT alone or combined modality therapy demonstrated that, regardless of RT dose, most failures were not in the initial radiation field but in contiguous unirradiated sites (Kamath et al. 1999). While a dose of 30 Gy provided sufficient control for patients with non-bulky, intermediate- and high-grade NHL who had a CR to initial chemotherapy, fewer in-field recurrences were seen with a dose of at least 40 Gy for patients with bulky disease or non-CR to initial chemotherapy. In a phase III randomized trial from the UK comparing different RT doses for NHL, patients with aggressive NHL (predominantly DLBCL) were randomized to 40–45 Gy in 20–23 fractions versus 30 Gy in 15 fractions (Lowry et al. 2011). There were no differences in overall response rate, in-field progression, PFS, or OS between arms. Regarding radiation fields, while IFRT has been historical standard in large-scale trials, a retrospective study by Campbell et al. evaluated outcomes of patients with limited-stage DLBCL treated with 3 cycles of systemic therapy (primarily CHOP, ~15% R-CHOP) followed by consolidative IFRT versus INRT (Campbell et al. 2012). In-field and marginal recurrences were minimal (1–2%) and not significantly different between RT fields. PFS and OS were also not significantly different between patients treated with IFRT versus INRT. The most recent guidelines from ILROG endorse and outline field designs for ISRT for NHL, using CT- or PET-CT-based treatment planning, 4D CT simulation, and IMRT with image guidance (Illidge et al. 2014).

Taken together, improved outcomes with consolidative RT added to R-CHOP, along with more conformal, lower-dose RT that should limit toxicities and side effects, strongly suggest that combined modality treatment with R-CHOP systemic therapy followed by consolidative ISRT should be standard of care for limited-stage DLBCL pending future randomized prospective studies. Per the most recent American College of Radiology (ACR) appropriateness criteria for DLBCL, factors such as IPI score, presence of bulky disease, pathologic features, and response to initial systemic therapy should be considered when deciding the number of cycles of systemic therapy and dose of RT (Dabaja et al. 2015a).

Conclusion

Despite countless studies establishing the importance of radiation therapy in local control for both HL and NHL, controversy surrounding its use in certain patient populations still exists,

in large part because of concerns of late toxicity resulting in morbidity and mortality in lymphoma survivors. Indeed, an overall survival benefit is often not seen with RT, in part due to late effects from historically more extensive treatment fields. Advances in imaging and treatment delivery that allow for more conformal RT delivered to smaller fields with lower doses should continue to reduce long-term toxicity from RT dramatically. At the same time, efforts to identify which patients would benefit most from RT, using pretreatment predictive factors and mid-treatment response assessment, will provide further guidance on the development of individually tailored treatment regimens that incorporate RT in the most beneficial manner. Continued investigation on radiation field size, dose, and advanced delivery techniques is needed to ensure clinical efficacy is not compromised with treatment de-intensification and increased conformality. Ultimately, further study on the selective integration of RT is needed to optimize the therapeutic ratio for patients with HL and NHL.

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Brain Metastases

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Abstract

Brain metastases (BM) cause significant morbidity and mortality, with profound personal and societal impact. Historically, surgery and whole-brain radiotherapy (WBRT) were the mainstays of management. WBRT alone has been shown to have limited role for durable local control, and there are concerns regarding its impact on quality of life (QoL) and neurocognitive function. Advances in systemic therapeutics have afforded improved control of extracranial disease and paved the way for improved survival outcomes. In parallel, the overarching goals of BM management are to provide durable intracranial control and good QoL, with minimal long-term toxicities, and, if possible, to prolong survival. However, there remain significant controversies within the oncology community about how these goals should be achieved. Herein, we will review various management strategies, including the role of stereotactic radiosurgery (SRS) and methods to mitigate long-term toxicity of WBRT.

1 Introduction

BM are the most commonly encountered intracranial malignancy within the radiation oncology clinic. It is estimated that up to 40% of cancer patients (Nussbaum et al. 1996) will develop BM in their lifetime. Certain cancer primaries have a predilection to seed the brain, accounting for up to 80% of BM – these include primary lung, melanoma, breast, and renal cell cancers (Barnholtz-Sloan et al. 2004).

In the United States alone, there are an estimated 170,000–200,000 new cases of BM reported each year (Fox et al. 2011). Furthermore, the incidence of BM is expected to increase over time (Smedby et al. 2009). This is likely for a few reasons:

1. The onset of the silver oncologic tsunami: an aging population, buttressed by a rising incidence of cancer in those above 65 years (Chapman et al. 2015)
2. Improved systemic therapeutics which provide extracranial disease control, but fail to address BM
3. Improved diagnostic capabilities, including thin-slice magnetic resonance imaging (MRI) with volumetric reconstruction, to detect smaller lesions in asymptomatic patients
4. Improved reporting of cases, through better access to healthcare and early referrals

BM, unfortunately, carry a high mortality rate with the median survival historically being below 4 months (m) (DiStefano et al. 1979). As a result, the detection of BM has been the cue for many to assume a fatalistic approach, withholding aggressive treatment in a patient who is believed to have a poor outcome regardless. The routine use of WBRT has been the mainstay, and the potential treatment-related toxicities largely dismissed.

In more recent years, advances in neurosurgery, neuroimaging, systemic therapeutics, and radiation therapy have afforded longer survival in some patients, especially those with good performance status and prognostic factors (Sperduto et al. 2012). For example, the 1-year survival for patients treated between 1983 and 1989 was 15%, compared to 34% for patients treated between 2005 and 2009 (Nieder et al. 2011). As a result, there has been heightened concern about the routine use of WBRT and its attendant long-term (and often irreversible) toxicities. This has led to considerable dissonance within the oncology circle regarding the appropriate management of BM – especially with society's increasing focus of neurocognition and QoL. Consequently, in the absence of strong evidence, many centers have adopted SRS alone, as the preferred treatment option, in patients with multiple BM (Sneed et al. 1999; Hasegawa et al. 2003).

This chapter sets out to review the evolving literature and seminal trials that have shaped the

landscape in the management of BM. In particular, we will place emphasis on neurocognitive function and ways to mitigate late toxicities.

2 History and Evolution

2.1 WBRT

Prior to the advent of WBRT, survival of patients with BM was typically 1–2 m with corticosteroids alone (Vecht et al. 1994; Wolfson et al. 1994). Although steroids produced temporary symptom relief, invariably all patients died secondary to intracranial disease progression.

WBRT came to the forefront as the recommended treatment after the seminal publication by Chao in 1954 (Chao et al. 1954). In their publication, they suggested doses of 30–40 Gy achieved symptomatic relief in 24 of the 38 patients (63%), with about half living slightly over 3 months. Interestingly, WBRT has never been evaluated, until recently, in a randomized clinical trial against supportive care alone. However, its wide reach, ease of administration, and relatively low cost have made it the de facto treatment for patients with BM.

Much focus, primarily through RTOG, was placed on comparing various dose-fractionation schedules of WBRT (Harwood and Simson 1977; Kurtz et al. 1981; Borgelt et al. 1980, 1981; Chatani et al. 1986; Haie-Meder et al. 1993; Murray et al. 1997). Unfortunately, there was no survival benefit seen among the various tested regimens. Moreover, 27–54% of patient continued to die from neurological death (presumably from intracranial progression) despite having undergone WBRT (Borgelt et al. 1980).

The lack of a dose-response for survival can be attributed to two reasons:

1. The brain parenchyma is a radiosensitive structure, and the tested doses were mostly subtherapeutic for durable disease control (i.e., intracranial failure).
2. Patients succumbed to uncontrolled systemic disease instead. (i.e., extracranial failure).

In any case, these studies reiterated the fact that WBRT provides excellent palliation to patients with BM, with approximately 60% achieving relief of symptoms (such as headache, motor function, impaired mentation) by the end of week 2 (Borgelt et al. 1980).

2.2 SRS

SRS has emerged as an optimal form of focal therapy to treat BM. The characteristics of BM, namely, spherical shape, well-demarcated margin, and absence of normal brain parenchyma inside the tumor volume, lend themselves well for SRS. The ability to deposit an ablative dose in a focused manner while avoiding collateral damage to brain parenchyma has made it a valuable tool. Moreover, the large ablative doses utilized allow for superior control rates possibly through endothelial damage (Garcia-Barros et al. 2003) and immune-mediated mechanisms (Burnette et al. 2011; Lee et al. 2009).

The first report of SRS dated back to 1950, by a Swedish neurosurgeon (Dr Lars Leksell) (Leksell 1951). Subsequently in 1987, Sturm reported on the use of linear accelerator-based SRS techniques (Sturm et al. 1987). The RTOG 90-05 phase I dose-escalation study (Shaw et al. 2000) set the stage for the maximum-tolerated dose, which was determined by lesion size, and is still being followed today. In the modern setting, SRS platforms have become ubiquitous, and there have been multiple commercial options to deliver SRS. These include Gamma Knife (Elekta AB, Stockholm, Sweden), CyberKnife (Accuray Inc., Sunnyvale, USA), Novalis (Brainlab AG, Germany), TomoTherapy (Accuray Inc., Sunnyvale, USA), and Proton therapy.

SRS has allowed for a paradigm shift in the way BM are managed. This is evidenced by the exponential increase in its use in the twenty-first century (Halasz et al. 2013). The main advantages of SRS over WBRT are the sparing of most of the brain parenchyma, its single-session outpatient delivery facilitating minimal downtime, patient convenience, and ability to commence systemic therapy sooner. In addition, there remains an option to repeat the procedure to additional lesions that may surface subsequently, obviating the need for WBRT.

3 How Should We Treat Patients with Limited BM?

In patients who are expected to survive longer, sustained intracranial control becomes essential to prevent demise from local progression (i.e., neurological death). Historically, WBRT alone, as mentioned earlier, had been the mainstay treatment. However, it is unlikely to provide sustained control. Response of BM to WBRT is related to lesion size, underlying histology and dose. Nieder et al. (1997) demonstrated that complete radiological remission to WBRT differed by histology – 37% for small-cell carcinoma, 35% for breast cancer, 25% for squamous cancer, and 14% for non-breast adenocarcinoma. The size of the underlying lesion significantly influenced response rate (52% for lesions below 0.5 cc and 0% for lesions above 10 cc). A second study by Nieder et al.(1998) showed that partial remission rates improved with increasing biological effective dose; however, we are limited by the whole-organ radiation tolerance.

Taken together, the above studies suggest that long-term control of gross BM is unlikely with WBRT alone. A case in point of the suboptimal control would be the dismal 1-year control rates (0–14%) from the randomized controlled trials (RCT) performed by Kondziolka et al. (1999) and Patchell et al. (1990). This is concordant even in more recent trials with regular MRI surveillance, such as RTOG 0933, which reported the median progression-free survival to be 5.9 m (95% CI 4.7–8.4 m)

3.1 Surgery + WBRT Versus WBRT Alone

Intuitively, surgical resection of bulky BM provides immediate and effective palliation of symptomatic mass effect. Moreover, it can also provide histological confirmation of the diagnosis when it has not yet been established. However, there was equipoise in the benefits of addition of surgery to WBRT. To date, three RCTs have been conducted on the premise that improved local control would result in improved overall survival. Notably, all three trials only included patients with single BM.

Patchell et al. conducted a single-center randomized trial ($n = 48$), investigating the survival benefit of surgical excision plus WBRT versus WBRT alone (36 Gy in 12 fractions) (Patchell et al. 1990). All patients had good performance status (KPS > 70), and only a third (37.5%) had extracranial disease. The investigators reported a significant survival benefit with surgery (median survival 40 vs 15 weeks, $P < 0.01$). Moreover, patients treated with surgery maintained functional independence for a longer period (38 vs 8 weeks, $P < 0.005$).

Noordijk et al. conducted a similar multicenter randomized trial ($n = 66$), except that WBRT was delivered bi-daily (40 Gy in 20 fractions, over 2 weeks) (Noordijk et al. 1994). A survival benefit was, once again, demonstrated with the addition of surgery (10 vs 6 m, $p = 0.04$). However, subgroup analysis showed that the survival difference was present only in the patients (70%) with inactive extracranial disease (12 vs 7 m, $P = 0.02$; 5 m in the group with progressive extracranial disease irrespective of treatment arm).

Mintz et al. reported their trial ($n = 84$), which had similar study arms (Mintz et al. 1996). 30 Gy of WBRT was delivered over 10 fractions. Unlike the above 2 trials, this trial included a larger proportion of patients (45%) with extracranial disease and a sizeable portion (21.4%) who were of KPS 50–60. This was a negative trial, as they failed to find a survival benefit with surgery (5.6 vs 6.3 m, $P = 0.24$). Extracranial disease was reported to be a significant prognostic factor for mortality.

From the above studies, it is clear that patient selection remains important and survival gains may be diminished in patients with active extracranial disease or poor performance status.

3.2 SRS + WBRT Vs WBRT Alone

Trialists investigated whether similar benefits may be seen in patients treated with SRS, instead of surgical excision. A number of RCTs have addressed this question. Notably, they allowed up

to 4 lesions (which was chosen arbitrarily) and addressed varying endpoints.

The first of these trials, from the University of Pittsburgh (Kondziolka et al. 1999), randomized 27 patients who were KPS > 70 and had 2–4 metastases (below 2.5 cm) to WBRT alone (30 Gy in 12 fractions) or WBRT plus SRS (16 Gy). This trial was stopped early, as there was significant local failure without SRS (local failure 100% vs 8%). There was no difference in overall survival (OS) (7.5 vs 11 m $P = 0.22$), but it was possibly due to the lack of power. Once again, extent of extracranial disease emerged as a significant prognostic factor for survival.

Chougule et al. conducted a single-institution RCT (Chougule et al. 2000) for patients with 1–3 metastases and tumor volume below 30 cc. They were randomized to WBRT alone (30 Gy in 10 fractions) or WBRT plus SRS 20 Gy. Although published only in abstract form, local control was improved with SRS (91 vs 62%).

The strongest evidence for this strategy comes from the multi-institutional, RTOG 95-08 trial (Andrews et al. 2004) ($n = 331$). Patients with 1–3 metastases were randomly allocated to WBRT alone (37.5 Gy in 15 fractions) or WBRT followed by SRS boost. The SRS dose followed findings from the RTOG 9005 trial: 24 Gy up to 2 cm, 18 Gy for 2–3 cm, and 15 Gy for 3–4 cm. The primary outcome, OS, was not different between the 2 arms (6.5 vs 5.7 m, $P = 0.13$). However, subgroup analysis suggested that patients with single BM ($P = 0.04$) and/or age < 50 ($P = 0.04$), non-small-cell histology ($P = 0.05$), and RPA class 1 ($P = 0.05$) have a survival advantage with the addition of SRS. Local control rates, as expected, were improved with SRS boost ($P = 0.01$). However, the multiple unplanned subgroup analysis has been criticized as it increases the type 1 error rate. A secondary analysis (Sperduto et al. 2014), post-stratified by GPA, was performed ($N = 252$). Overall, the primary conclusion was not different from the earlier study. However, subset analysis revealed survival improvement (median survival SRS + WBRT 21 m vs 10.3 m WBRT alone, $P = 0.05$), only in good prognostic patients (GPA 3.5–4).

The above trials categorically proved that local control was improved with the addition of SRS to WBRT. For the purist who does not believe in subgroup analysis, none of the trials showed any improvement in survival with the addition of SRS.

3.3 Surgery Alone Vs Surgery + WBRT

The question of whether one could use focal therapy alone for BM was addressed in a number of clinical trials, focusing on outcomes including survival, neurocognitive function, and QoL. The key findings are summarized in Table 1.

Patchell et al. (1998) conducted the seminal RCT to determine if adjuvant WBRT is beneficial after excision of a single BM. Ninety-five patients with single BM were randomized to WBRT (50.4 Gy in 28 fractions) or observation after surgical resection. The primary endpoint of this trial was intracranial recurrence. WBRT group had reduced intracranial recurrence compared to observation (18 vs 70%, $P < 0.001$). Both local and distant recurrences were reduced by WBRT (10 vs 46%, $P < 0.001$; 14 vs 37%, $P < 0.01$). Although WBRT reduced neurological death, OS was not different. This trial proved that surgery alone for single BM is suboptimal and WBRT can reduce the risk of intracranial failure.

3.4 SRS Alone Vs SRS + WBRT

An early retrospective study addressing this question was published by Pirzkall and colleagues (1998). They performed a retrospective comparison of 236 patients (158 of whom received SRS alone 20 Gy, 78 received SRS 15 Gy followed by WBRT). The OS was not significantly different between both groups; however, for patients without extracranial disease, median survival was improved with WBRT (15.4 vs 8.3 m, $P = 0.08$). There was also a suggestion that higher doses of SRS resulted in improved outcomes. This study is often quoted as the basis to routinely offer WBRT in addition to

Table 1 Randomized Controlled Trials investigating surgery or SRS alone compared to surgery or SRS + WBRT

Author (year)	*N*	Median follow-up	Included patients	Primary endpoint	Local failure	Distant brain failure	Salvage therapy	Survival	Functional outcomes
Surgery vs surgery + WBRT									
Patchell et al. (1998)	95	43 weeks	Single BM KPS ≥ 70	Brain tumor recurrence	10 vs 46% ($P < 0.001$)	14 vs 37% ($P < 0.01$)	NR	48 vs 43 weeks ($P = 0.39$)	NR
Kocher et al. (2011)	160	40 m	1–3 BM ECOG 0–2 Stable systemic disease or asymptomatic synchronous primary	Duration of functional independence (ECOG ≥ 2)	27 vs 59% ($P < 0.001$)	23 vs 42% ($P = 0.008$)	16 vs 51%	10.9 vs 10.7 months ($P = 0.89$)	HRQOL better in observation arm
SRS alone vs SRS + WBRT									
Aoyama et al. (2006)	132	7.8 m	1–4 BM (<3 cm) KPS ≥ 70	OS	88.7 vs 72.5% ($P = 0.002$)	41.5 vs 63.7% ($P = 0.003$)	15 vs 43% ($P < 0.001$)	1 year actuarial survival 38.5% vs 28.4% (SRS alone) ($P = 0.42$)	No difference in MMSE or neurological functional preservation
Chang et al. (2009)	58	9.5 m	1–3 BM RPA 1–2 KPS ≥ 70	Neurocognitive function, measured by HVLT-R total recall at 4 m	67 vs 100% ($P = 0.012$)	45 vs 73% ($P = 0.02$)	0 vs 27%	1 year survival 21 vs 63% (SRS alone) ($P = 0.003$)	HVLT-R total recall mean posterior probability of decline 24 vs 52%
Kocher et al. (2011)	199	40 m	As above	Duration of functional independence (ECOG ≤ 2)	19 vs 31% ($P = 0.04$)	33 vs 48% ($P = 0.023$)	16 vs 51%	10.9 vs 10.7 months ($P = 0.89$)	HRQOL better in observation arm
Brown et al. (2016a)	213	7.2 m	1–3 BM (<3 cm)	Decline in >1SD , at 3 months, from baseline of any 6 cognitive tests	18.4 vs 7.4% at 6 m ($P = 0.034$)	11.6 vs 35.4% at 6 m ($P < 0.0001$)	7.8 vs 32.4% ($P < 0.001$)	Median OS 7.4 vs 10.4 m (SRS alone) (HR 1.02, $P = 0.92$)	Decline in cognition more in WBRT group (31 vs 8%, $P = 0.007$)

SRS. However, this study has several shortcomings, besides its retrospective nature. Patients from this study were treated between 1984 and 1997, when effective systemic therapy was likely unavailable. This is evidenced by the relatively short OS of the entire group (5.5 m). Secondly, the study design allowed either CT or MRI surveillance. As a result, early salvage may not have been instituted in patients who underwent CT surveillance, resulting in a survival difference.

Subsequently, a few prospective trials were conducted to address this question.

Aoyama reported the trial conducted by JROSG 99–1 (Aoyama et al. 2006), for which the primary outcome was OS. Investigators had planned to randomize 178 patients to detect a 30% difference in median survival time with a power of 80%. However, after interim analysis of 122 patients, the trial was terminated early as it was deemed unlikely to detect a difference in survival, and the outcome changed to brain tumor recurrence rate. In the end, 132 patients, with 1–4 lesions, were randomized to SRS alone or SRS plus WBRT (30 Gy in 10 fractions). SRS dose depended on tumor size (22–25 Gy for up to 2 cm, 18–20 Gy for 2–3 cm, dose reduced by 30% in WBRT group). Fifty percent of patients were above 65 years, and up to 50% had active extracranial disease (primary or metastasis). The 1-year survival rate was not different between the 2 arms (38.5 vs 28.4%, $P = 0.42$). As expected, the brain tumor recurrence rate was less with WBRT (46.8 vs 76.4%, $P < 0.001$). As a consequence, the SRS alone group required more salvage procedures (43 vs 15%, $P < 0.001$). However, this did not translate to a significant difference in systemic ($P = 0.53$) and neurological ($P = 0.99$) functional preservation. Unlike the Patchell trial, and despite the higher brain tumor recurrence rates, neurologic death was not reduced with WBRT (22.8 vs 19.3%, $P = 0.64$). The actuarial 12 m local control rates were significantly higher with WBRT (88.7 vs 72.5%, $P = 0.002$). This may be in part attributed to the advantages of fractionation in overcoming radiation resistance.

Neurocognitive testing (not a secondary endpoint) was performed optionally using Mini-Mental State Examination (MMSE) (Aoyama et al. 2007). Of the 82 patients with MMSE scores >27, or whose scores improved to >27 after treatment, there was no difference in the preservation of MMSE rate (log-rank $P = 0.73$ and 0.79, respectively). The average duration before MMSE deterioration was longer in the WBRT group (16.5 m vs 7.6 m, $P = 0.05$). The authors suggested that this difference may be due to the preventive effect on brain tumor recurrence from WBRT. These data also showed that for patients treated with SRS alone, deterioration in MMSE scores from intracranial relapses returned to baseline after salvage therapy compared to treatment-induced deterioration in MMSE score after WBRT plus SRS, which was refractory to medical and other interventions. However, no strong conclusions can be drawn from this. Firstly, the number of remaining patients was exceedingly small (i.e., in total 21 patients at 12 m, 10 patients at 24 m). Secondly, MMSE is a relatively crude and insensitive instrument to detect any change in neurocognitive function. Thirdly, patients for whom no follow-up MMSEs were available were excluded, introducing bias from incomplete outcome data.

A secondary analysis of this trial was published in 2015 (Aoyama et al. 2015). Eighty-eight patients with non-small-cell lung cancer (NSCLC) were post-stratified by disease-specific GPA (ds-GPA), to reduce bias pertaining to underlying histology. Authors report an improvement in survival with the addition of WBRT, for patient with better prognosis (ds-GPA 2.5–4). In this group of 47 patients, median survival was 16.7 m versus 10.6 m ($p = 0.04$). No difference in survival was seen for the group with poorer prognostic scores (DS-GPA 0.5–2), HR 1.05 (95% CI 0.55–1.99). Advocates of routine WBRT would cite this study as evidence that WBRT should be offered to patients with a better prognostic score. Others would argue that irreversible long-term toxicities are most likely in this group of potential long survivors, and hence WBRT should be avoided. Once again, it has to be noted that this is a post hoc analysis based on a small subgroup of patients and is subject to bias.

The EORTC conducted a prospective phase III trial (22952–26,001) (Kocher et al. 2011) comparing the addition of WBRT (30 Gy in 10 fractions) after initial surgery or SRS for patients with up to 3 BM, stable systemic disease, and asymptomatic primary. In total, 359 patients (199 SRS, 160 surgery) were included. The primary endpoint of the trial was time to deterioration of performance status (WHO ECOG >2), and the secondary endpoints included intracranial relapse, PFS and OS, and QoL. Patients with progressive systemic disease were excluded, but restaging scans were not mandated. There was no difference in the median time to deterioration of PS (10 m with observation vs 9.5 m with WBRT, HR = 0.96, $P = 0.71$). There was also no difference in OS (10.9 m vs 10.7 m, HR = 0.98, $P = 0.89$). As anticipated, WBRT reduced intracranial progression at initial sites, as well as distant intracranial sites. However, impact on local progression was more pronounced in the surgical group (59–27%, $P < 0.01$; SRS group 31–19%, $P = 0.04$). There were fewer deaths from intracranial progression in the WBRT arm (44 vs 28%). The lack in difference in OS has been criticized, due to the possible influence of extracranial progression and the absence of systematic restaging scans prior to randomization. However, in support of the trial findings, it has to be noted that the incidence rates of extracranial progression were not different in both arms (63% vs 65%, $P = 0.73$).

QoL results were assessed systematically by EORTC C30 and Brain Tumor Module, with a ≥10 point drop from baseline being considered clinically relevant (Soffietti et al. 2013). Understandably, compliance rates were low at the end of the first year (45%). Overall, patients on the observation arm had improved health-related QOL (HRQOL) scores compared to patients who underwent adjuvant WBRT.

Self-reported HRQOL (compared to a formal battery of neurocognitive tests) is not as sensitive for neurocognitive function per se; nevertheless, HRQOL is an increasingly important endpoint for patients and physicians alike. However, the high noncompliance rate affects the validity of these findings. It is interesting to note that although WBRT reduced intracranial progression, this did not translate into improved HRQOL for the patients. This is likely due to the early detection of asymptomatic relapses and the use of effective salvage therapy.

Chang et al. conducted a single-institution RCT comparing SRS ± WBRT (30 Gy in 12 fractions), for which the primary endpoint was neurocognitive function. This was assessed methodically by Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months post-treatment (Chang et al. 2009). The trial was stopped early, after 58 patients were randomized as there was a 96% probability that patients undergoing WBRT were significantly more likely to show a decline in learning and memory function. As one would expect, a larger proportion of patients who underwent WBRT were free of CNS recurrence at 1 year (73 vs 27%, $P = 0.0003$). Although this trial was not powered to detect any survival differences, the median survival was worse in the arm undergoing WBRT (5.7 vs 15.2 m). This reason for this survival difference remains unclear, although the WBRT group had a slightly higher incidence of visceral disease (18 vs 7% liver metastasis, 18 vs 10% adrenal metastasis). Critics of this trial also point out that neurocognitive outcomes were measured at a single, and relatively early, time point; therefore, recovery of neurocognitive function after 4 months may not be reflected (Onodera et al. 2014).

Findings from the above trial were corroborated by the NCCTG N0574 (Alliance) trial (Brown et al. 2016a). The highlight of this trial is that it addressed neurocognition (via healthcare staff-administered battery of cognitive tests) and QoL at multiple time points. Two hundred thirteen patients (68% lung primary), with 1–3 BM (50% single lesion), were enrolled from 34 institutions. Patients in the SRS alone received 24 Gy (for lesions less than 2 cm) or 20 Gy (for lesions 2–2.9 cm). Patients in the combined modality arm received WBRT 30 Gy in 12 fractions with SRS 22 Gy (up to 2 cm) or 18 Gy (2–2.9 cm). The primary outcome of this trial was determined if the cognitive progression 3 months post SRS was worse with WBRT. This was defined as a drop by

>1 standard deviation from baseline, in any of the 6 cognitive tests. In keeping with previous studies, WBRT decreased intracranial progression (6 m progression rate 35.4% vs 11.6%, $P < 0.0001$), but did not impact OS (median 10.4 m SRS alone, 7.4 m WBRT + SRS, HR 1.02 $P = 0.92$). Despite having less intracranial progression, there was significantly more cognitive decline at 3 months in the WBRT arm (91.7% vs 63.5%, $p = 0.007$). Interestingly, this difference persisted at 6 months (97.9% vs 77.8%, $P = 0.03$). The specific domains which seemed to be affected include immediate recall (30 vs 8%), delayed recall (51 vs 20%), and verbal fluency (19 vs 2%). There were also significantly worse QoL measures with WBRT, which is in keeping with the EORTC trial findings.

The above studies have provided evidence required for a change in practice. The American Society for Radiation Oncology (ASTRO) has come out strongly to make a recommendation not to routinely add WBRT to SRS, for patients with limited BM, in their Choosing Wisely Campaign (http://www.choosingwisely.org/astro-releases-second-list/). The National Comprehensive Cancer Network (NCCN) has recently revised its guidelines to include SRS alone in this group of patients, for which the upper limit of BM number was left unspecified.

For patients undergoing the SRS alone approach, all trials have indicated that they have a higher incidence of salvage therapy. Therefore, close monitoring, with regular surveillance MRI, is critical. Based on the Aoyama series (Aoyama et al. 2006), only 16% of patients were symptomatic for their recurrences, and early salvage did not result in a difference in neurologic deterioration or death between the 2 arms. In contrast, neurological deficits may not recover fully if detected late. For example, the retrospective single-institution study by Regine et al. (2002) showed that 70% of patients developed symptomatic recurrences (after SRS alone), and this was associated with a 50% neurologic deficit progression-free survival at 1 year. As such, one may interpret that withholding WBRT without close surveillance (and early salvage) does more harm than WBRT itself.

3.5 Surgery vs. SRS

High-quality evidence comparing the two modalities is lacking. Empirically, most practitioners would favor surgery to establish histological diagnosis or obtain a rapid reduction in intracranial pressure. On the other hand, SRS has distinct advantages such as ability to address lesions within eloquent areas, outpatient delivery with minimal downtime, potentially lower costs, and avoidance of surgical and anesthetic risk.

Bindal et al. (1996) reported a retrospective matched comparison between surgical resection and SRS (2:1 matching, 93 patients). Interestingly, the group that underwent surgical resection had twice the median survival (16.4 vs 7.5 m, $P = 0.0016$); and treatment received was a significant factor in multivariate analysis. Local recurrence rates were lower with surgery (21 vs 8%), and the surgical group has a lower chance of death through neurological progression (50 vs 19%). According to the authors, the difference in the two groups was not attributable to the use of WBRT, which was similar in both groups. Although intriguing, the retrospective nature of this study and the lack of matching for tumor size suggest that these results should be interpreted with caution. Moreover, the radiosurgery doses used in these patients were lower than those used in the RTOG studies, which may account for the higher rates of local progression.

On the contrary, Rades et al. (2009) suggested that 1-year OS was improved with the use of SRS + WBRT compared to surgery + WBRT (56 vs 47% $P = 0.034$), for patients with 1–3 BM. Local control rates were also superior in the SRS arm (82 vs 66%, $P = 0.006$).

Owing to the retrospective nature of the above studies (although matching was performed for key factors), patient selection bias may have led to confounding of the results. Unfortunately, there is a dearth of prospective studies addressing the above question.

Muacevic et al. (Muacevic et al. 2008) reported the results of their RCT comparing microsurgery + WBRT (40 Gy) to SRS for patients with single BM (<3 cm). The study was closed prematurely due to poor accrual. At final

analysis, there were 33 patients in the surgical arm and 31 patients in the SRS arm. There were no significant differences in survival, neurological death rate, or freedom from local recurrences between the 2 arms. The SRS alone arm had higher distant recurrences ($P = 0.04$), but this difference was not significant after adjustment for salvage SRS ($P = 0.4$). The conclusions drawn from this trial are limited, due to the lack of statistical power.

Similarly, Roos and colleagues (2011) attempted to conduct a randomized non-inferiority trial to determine whether SRS + WBRT was as effective as surgery + WBRT in patients with solitary BM. However, this trial faced slow accrual which was closed prematurely. Twenty-one patients were analyzed, and the estimated median survival in the SRS arm was 6.2 m compared to 2.8 m (HR 0.53, 95% CI 0.2–1.43, $P = 0.2$). Like the above trial, the lack of statistical power precludes any valid conclusion being made.

3.6 Cavity SRS as an Alternative to WBRT or Observation

Investigators realized that local recurrences continued to be a significant problem after surgical resection of BM (Patchell et al. 1998; Kocher et al. 2011). WBRT was able to reduce local recurrences, but failed to impact OS. Pioneering work for resection cavity SRS was performed by the Stanford group, which suggested that SRS to the resection bed were able to provide similar local control rates without causing the dreaded long-term toxicities. For example, they had retrospectively reported the outcomes of 72 patients (76 cavities) whom underwent SRS (median marginal dose 18.6 Gy) with the resection cavity volume ranging from 0.1–66.8 cm^3 (mean 9.8cm^3) (Soltys et al. 2008). Actuarial control rate at 12 months was 79%, which was comparable to historical WBRT series (80–90%) and superior to observation alone (54%). Surprisingly, the group with the least conformal plan had the best control rates, suggesting that marginal misses through delineation errors, or local tumor infiltration, may be contributory.

A follow-on study was published by Choi et al. (2012). Outcomes of patients treated with resection cavity SRS, with or without a 2 mm margin, were reported retrospectively. One hundred twelve patients (120 cavities) had a 12-month cumulative local failure rate of 9.5% and distant failure rate of 54%. The addition of a 2 mm margin decreased local failure rates from 16% to 3% ($P = 0.042$), without causing more toxicities (3 vs 8%, $P = 0.27$).

A phase II prospective study was conducted at MSKCC (Brennan et al. 2014). Forty-nine patients (50 lesions) with 1–2 BM were enrolled. Forty lesions received postoperative SRS with a median dose of 18 Gy. The cumulative local failure at 12 months was 22%, and regional failure was 44%. Compared to deep brain lesions <3 cm, superficial lesions ≥3 cm had a high local failure rate at 53.3% at 12 months.

Although this is a promising and novel approach, one should be cautious before universal adoption. Two phase III trials were presented at the 2016 ASTRO annual meeting. The first is a prospective randomized trial, from MD Anderson Cancer Center, comparing cavity SRS to observation for completely resected BM (Rao et al. 2016). The primary objective of this trial was local tumor control. One hundred twenty-eight were randomized (63 SRS, 65 observation) with a median follow-up of 13 m. As one would expect, the local control at 12 months was improved with SRS (72 vs 45%, HR 0.46 95% CI 0.25–0.85, $P = 0.01$). However, there was no difference in distant BM (HR 0.79, 95% CI 0.5–1.24, $P = 0.29$) or overall survival (HR 1.22 95% CI 0.79–1.87, $P = 0.37$). The incidence of leptomeningeal dissemination was similar in both arms (HR 1.4, 95% CI 0.6–3.4, $P = 0.46$). The second is NCCTG N107C/RTOG 12-70 trial, which is a multicenter RCT comparing postsurgical SRS to WBRT, where one of four (or fewer) lesions has been resected (Brown et al. 2016b). The primary endpoints are OS and cognitive-deterioration free survival. One hundred ninety-four patients were randomized with a median follow-up of 18.7 m. OS was not different between the 2 arms (11.5 vs 11.8 m, HR 0.93 95% CI 0.66–1.3, $P = 0.65$). However, the arm

SRS had an improved cognitive-deterioration free survival (3.3 vs 2.8 m, HR 2.05, 95% CI 1.51–2.77, $P < 0.0001$). WBRT significantly improved overall intracranial control, compared to SRS alone, but was associated with more toxicities.

4 Does Number Really Matter?

The definition of patients with limited BM has been sought with controversy. The majority of phase III trials (Aoyama et al. 2006; Kocher et al. 2011; Chang et al. 2009; Brown et al. 2016a) only included patients with one to three or four BM. The upper limit of limited BM was set rather arbitrarily for technical reasons. Early trials utilized SRS planning software which lacked sophistication to calculate integral dose from overlapping plans, creating a safety concern for multiple lesions. Moreover, SRS for multiple lesions would have taken prohibitively long using older SRS platforms. Thankfully, modern day equipment (such as flattening filter-free linear accelerators) and planning systems are able to execute the planned treatment efficiently. Guidelines from major societies based their recommendations on level 1 evidence and consequently have only recommended SRS for up to four lesions (Tsao et al. 2012a; Kocher et al. 2014).

Knisely et al. (2010) published the results of a survey done on 149 physicians, from San Francisco and Sendai, practicing SRS. Surprisingly, 55% of respondents from San Francisco would consider treating ≥5 lesions with SRS, and this was even more pronounced for the respondents from Sendai (83% would consider treating ≥5 lesions). As such, it was clear that there was no consensus on the number of BM that is considered suitable for SRS. The question really is, whether BM number alone is a harbinger of worse prognosis?

Karlsson et al. (2009) reported a large multi-institutional retrospective study of 2448 Gamma Knife treatments administered between 1975 and 2007. The survival in patients with a single BM was longer than that of patients with multiple BM (7.5 vs 6.1 m, $P < 0.0001$). However, this difference was lost when adjusted for controlled primary disease. Moreover, there was no difference in survival between patients with 2, 3–4, 5–8, or >8 BM. The use of WBRT did not impact survival (7.4 m with WBRT, 7.0 m without, $P = 0.43$).

Yonsei University group have published their experience with SRS alone for multiple BM ($N = 323$). Patients were divided into four groups based on the number of BM (group 1, 1–5; group 2, 6–10; group 3, 11–15; and group 4, >15 lesions). 2/3 of patients belonged to group 1. Surprisingly, there was no difference in OS between the 4 groups (log-rank $P = 0.554$). However, the probability and time to developing new BM was highest in group 4 ($P = 0.014$).

The best evidence regarding the impact on BM number comes from a recent report from Yamamoto et al. (2014). A large multi-institutional prospective observational study (JLGK0901) was performed to investigate whether SRS (sans WBRT), as the initial treatment, for patients with 5–10 BM was non-inferior compared to 2–4 BM, with respect to OS. Patients with KPS 70 or higher, from 23 centers in Japan, with 1–10 BM were eligible (largest tumor <10 mL, <3 cm in longest diameter; total cumulative volume < 15 mL). Tumors smaller than 4 mL were irradiated to 22 Gy, whereas tumor 4–10 mL received 20 Gy. Of the 1194 patients enrolled, median OS was 13.9 m in 455 patients with one tumor, 10.8 m in 531 patients with 2–4 tumors, and 10.8 m in 208 patients with 5–10 tumors. OS did not differ between the latter two groups (HR 0.97 95% CI 0.81–1.18). This was lower than the prespecified non-inferiority margin of 1.3 ($P < 0.0001$). In terms of treatment-related toxicity, there was no significant difference between the groups (9% in both groups $P = 0.89$). As expected similar to other WBRT avoidance studies, there was a relatively high incidence of new BM (58%), which highlights the crucial importance of regular and systematic surveillance with MRI scans. In toto 9% of patients required salvage WBRT, and this did not differ between groups ($P = 0.48$).

The above study provides the largest body of evidence that BM number alone should not be

used as a strict cutoff. However, there are some limitations which we need to acknowledge.

Firstly, this was not a randomized study, and therefore imbalances in the treatment arms are likely to have confounded outcome. For example, more patients with 5–10 BM had received systemic therapy compared to 2–4 BM. Secondly, robust neurocognitive assessment was not performed in this study.

To date, WBRT is still favored by many practitioners when there are 5 or more brain metastases as there are no completed RCTs supporting the use of focal therapy alone. However, SRS alone is regarded as maybe appropriate for patients with multiple metastases but small volume disease. According to National Comprehensive Cancer Network (NCCN) guidelines, SRS alone in patients with more than 3 metastases is still regarded as a good option if they have good performance status and low overall intracranial tumor volume.

A recently completed multi-institution propensity-matched retrospective study (Halasz et al. 2016) comparing SRS alone to WBRT alone suggests that survival is improved with SRS (adjusted HR 0.58, 95% CI 0.38–0.87) for patients with <4 metastases. This should be interpreted as hypothesis generating and should be confirmed by a randomized clinical trial.

The North American Gamma Knife Consortium NAGKC12–01 (NCT01731704) planned to conduct a RCT comparing WBRT 30 Gy in 10 fractions to SRS alone in patients with >5 BM. Unfortunately, this trial was closed prematurely.

Many reports have suggested that the patient's prognosis is influenced more by tumor volume, rather than absolute number. The earliest report came out of University of Pittsburgh (Bhatnagar et al. 2006), where outcomes of patients with ≥4 BM were published. In multivariate analysis of the 205 included patients, total treatment volume (sum of the volume of all treated BM) turned out to be significant for OS ($P = 0.002$), whereas the number of intracranial metastasis was not ($P = 0.33$). This study provided a hypothesis-generating concept to be explored further.

Likhacheva et al. (2013) and colleagues corroborated this finding in their report. Total tumor volume > 2 cm^3 was a significant predictor of OS (HR 1.98, $P < 0.001$) and local control (HR 4.56). However, the number of BM was not predictive for distant brain failure, local control, nor OS.

From the above reports, it was not clear if total BM volume should be considered as a continuous variable or best used as a categorical variable ($2cm^3$). Baschnagel et al. (2013) attempted to answer this question in their publication, assessing outcomes of 251 patients. The HR of total BM volume (continuous variable) on multivariate cox regression analysis was 1.04 (1.00–1.08, $P = 0.046$). When BM volume was dichotomized to above or below $2cm^3$, HR was 1.5 (1.1–1.93, $P = 0.008$). The number of BM, like in previous reports, was not a significant predictor of OS (HR 1.06 95% CI 0.99–1.13, $P = 0.098$).

One may conclude that the absolute number of BM is an arbitrary cutoff, which is often used, in SRS trials and guidelines. The definition of limited BM is under a state of flux, and focal therapy (with or without WBRT) may be offered to patients with good prognoses.

5 Is There Still a Need for Routine "Adjuvant" WBRT in the Modern Era?

There have been two main theories about the development of BM. The micrometastatic theory suggests that there is no entity such as a solitary BM. Microscopic deposits exist, which are undetectable on imaging, and the routine use of "adjuvant" WBRT enables control of these deposits. The reseeding theory suggests that new BM are deposited, over time, from active extracranial disease. In this scenario, routine "WBRT" adds toxicity without providing benefit.

The previously discussed trials (Aoyama et al. 2006; Kocher et al. 2011; Chang et al. 2009) have provided level 1 evidence that the addition of WBRT improves control of BM (i.e., compartmental control), but had little impact on survival. Meta-analysis is particularly useful tool to pool results of trials, which individually may have been underpowered to detect a survival difference. Two meta-analyses reiterated the effect of

improved compartmental control (by reducing distant and local brain recurrences) (Soon et al. 2014; Tsao et al. 2012b); but neither detected a survival improvement. Sahgal and colleagues went one step further, to conduct an individual patient data meta-analysis (Sahgal et al. 2015) of phase III trials (Aoyama et al. 2006; Kocher et al. 2011; Chang et al. 2009). Three hundred sixty-four patients (with KPS > 70) were included, where 51% were treated with SRS alone and 49% treated with SRS and WBRT. Age was found to be a significant effect modifier for survival (P = 0.04), in favor of SRS alone for patients below 50 years. Within this group, the hazard ratio was death which was incrementally reduced with younger age. No such differences were noted in the group over 50 years. Local control was improved, with WBRT, across both age groups. However, age was once again a significant effect modifier for distant brain failure (P = 0.043). WBRT reduced the risk of distant brain failure in the older group, with incremental benefits seen with increasing age. The authors hypothesized that exposing patients below 50 to the adverse effects of WBRT, without having therapeutic gain, may explain the differences noted in survival. However, this provocative hypothesis requires further validation. It is to be noted that that patients below 50 only made up 19% of the pooled cohort. In addition, there was a higher proportion of patients in this group who had extracranial metastasis (58 vs 68%). Although the total number of deaths was larger in the WBRT group (84% vs 71%), the neurological deaths were lower (22 vs 39%). This may suggest that these patients were perishing due to progressive systemic disease.

Survival aside, WBRT improves compartmental control, but will everyone benefit from it equally? Several groups have suggested a risk-stratified approach to answer this question. Rodrigues et al. (2014) performed recursive partitioning analysis to determine the risk of regional failure (RF) and constructed a clinical nomogram, for patients who had undergone SRS alone (n = 361). Low risk (<25% 1-year RF) were classified as patients with a solitary lesion and above 55 years, intermediate risk (25–40% RF) as patients below 55 years and solitary lesions or WHO PS > =1 and 2–3 lesions, and high risk (>40% RF) as patients with WHO PS = 0 and 2–3 lesions.

A similar study was performed at Wake Forest University (Ayala-Peacock et al. 2014). They analyzed 464 patients, over a 10-year period, treated with SRS alone. Progressive systemic disease, number of metastases, discovery of new metastases at time of SRS, and histology were significant factors predicting time to distant intracranial failure. Among the histological subtypes included, melanoma and HER2-negative breast cancer were deemed to be of higher risk, as compared to HER2-positive breast cancer.

Although these models require external validation, a tailored approach may be suitable for patients deemed to have a high risk of distant intracranial failure. However, even in the high-risk group, it remains controversial if adjuvant WBRT would improve survival outcomes compared to SRS alone with early salvage.

6 What Are the Factors Determining Neurocognitive Function?

Neurocognitive function (NCF) has been increasingly used as the primary outcome in phase III trials in the last decade for a few reasons. Firstly, it has been demonstrated that cognitive function predicts survival (Johnson et al. 2012; Armstrong et al. 2011). Secondly, neurocognitive decline precedes imaging progression (Meyers and Hess 2003). Thirdly, NCF is a critical determinant of QoL (Li et al. 2008; Giovagnoli et al. 2005), and typically a drop in NCF is a harbinger for a drop in QoL. Lastly, it is an outcome that both patients and physicians place emphasis on and enables patients to function within the community and society.

Despite the merits, WBRT has come under scrutiny due to the increasing number of reports about its potential long-term, and often irreversible, effects on NCF. The first of these reports by DeAngelis et al. (1989) reported an 11% rate (5 of 47) of dementia at 1-year post-WBRT in survivors

without brain recurrence. The true incidence of neurocognitive dysfunction was not clear from this publication. Arguably, the incidence may be lower as all five patients received large fraction sizes (>3 Gy) and radiosensitizing agents. On the contrary, this was a retrospective case-finding methodology, and it is likely that only the severe cases would have been picked up. More recently, diffuse radiological periventricular white-matter changes have been reported to occur more frequently with WBRT (71.5%) than SRS (6.7%, $P < 0.0001$) (Stokes et al. 2015). Progressive white-matter changes have been correlated to neurocognitive decline, although not in the setting of radiation injury (Defrancesco et al. 2013; Hulst et al. 2013).

To be objective, NCF decline, albeit being negatively linked to WBRT, is multifactorial. Medications (such as steroids, chemotherapy), underlying psychosocial issues (such as fatigue, anxiety, depression), location and volume of underlying BM, and baseline NCF are likely suspects influencing eventual NCF. It is, however, not clear which of these factors has a higher attributable risk to NCF.

6.1 Intracranial Control Is Important for Neurocognitive Function

Evidence for the above came from an RTOG trial (Meyers et al. 2004) examining the addition of motexafin gadolinium to WBRT in patients with BM. This was the first collaborative trial to systematically examine NCF. 90.5% of patients had impairment of one or more neurocognitive tests at baseline, reiterating the fact that BM itself causes impairment in cognition. They found that impairment correlated with brain tumor volume but not number of BM, and predicted survival. Needless to mention, patients with progressive disease on MRI at 2 months continued to have neurocognitive deterioration. Surprisingly, even patients with partial response continued to have deterioration in most of the neurocognitive domains (except trail A and B tests). This may suggest that in addition to intracranial control, other factors (including WBRT) may contribute to the declining NCF. One shortcoming of this trial is that it failed to report outcomes beyond 2 months.

Another publication stemming from the above trial (Li et al. 2007) evaluated NCF in long-term survivors from the control arm (WBRT alone). One hundred thirty-five patients were assessable at 2 months and were dichotomized into good and poor responders. Time to NCF deterioration was improved among good responders, with significance seen in executive function and fine motor skills (but not memory). The differential impact on the various neurocognitive domains suggests that WBRT may particularly impair hippocampal-related functions such as memory and learning. This report suggested that disease progression was the main contributor to neurological decline. However, one has to note that all patients received WBRT in this trial, and it does not categorically answer the question about the harms of WBRT.

The last piece of evidence in support of this notion was from RTOG 9104 trial (Regine et al. 2001). This trial compared accelerated hyperfractionation to a standard treatment WBRT (30 Gy in 10 fractions) in 445 patients, of which 359 had MMSE performed. At 2 months, MMSE dropped 0.6 for patients with radiologically controlled BM, compared to 1.9 to those with uncontrolled BM ($P = 0.47$). However, at 3 months this was 0.5–6.3 ($P = 0.02$). Although this gives credence to the argument that uncontrolled BM leads to a decline in MMSE, the authors did not elaborate how radiological response was classified nor if the assessors were blinded.

6.2 WBRT or Intracranial Control?

The take-home message from the above reports is that failure to adequately control macroscopic disease leads to local intracranial progression, which in turn negatively impacts NCF and survival as a result of neurologic death. What remains unclear is the relative contributions of neurocognitive decline, between WBRT and intracranial progression.

In order to de-convolute the two competing risks, it is imperative that the scenario where

there is no macroscopic disease at baseline (i.e., prophylactic cranial irradiation PCI) should be examined. Gregor et al. (1997) assessed the impact of PCI in patients with limited-stage small-cell lung cancer. The authors failed to find a difference (at 1 year) between the two groups (PCI and no PCI). The PCI group was more likely to have worse verbal memory and sustained attention, although statistical significance was not reported. It is hard to draw conclusions from this study, in the absence of statistical reporting. Moreover, a wide range of PCI doses were allowed (physician's discretion), including 8 Gy in 1 fraction (13%).

A more contemporary phase III trial is RTOG 0214 comparing PCI (30 Gy in 15 fractions) versus observation in patients with locally advanced NSCLC (Gore et al. 2011; Sun et al. 2011). The primary endpoint was OS, and the secondary endpoints included NCF and QoL (measured using HVLT, MMSE, and activities of daily living scale). This trial was underpowered, as only 356 of the targeted 1058 patients were accrued. As a result, there was no difference in OS (HR 1.03 95% CI 0.77–1.36). However, the 1-year rates of BM were significantly different at 7.7 vs 18% (P = 0.004). Intuitively, from the above arguments, one would expect the group with less BM to have improved NCF and QoL. There was no statistically significant difference in QoL between the two arms; however, there was a trend for greater decline in patient-reported cognitive functioning with PCI. There was also a greater decline in HVLT in immediate recall (P = 0.03) and delayed recall (P = 0.08) in the PCI arm at 1 year. Therefore, in the absence of intracranial progression, these differences may be attributed to the treatment, namely, WBRT, rendered.

7 Management of BM in Patients with Poor PS or Asymptomatic Patients

There is significant equipoise about how best to treat patients with BM with a poor PS (KPS <50). Options include supportive care (with corticosteroids) or WBRT. The use of SRS for patients with poor PS is more controversial, with no RCT including patients with KPS <70.

Nieder et al. (2013) performed a matched retrospective analysis, involving 113 patients (median KPS 60, 80% RPA 3). Forty-one patients received supportive care alone, 41 patients received WBRT 30 Gy in 10 fractions, and 31 patients received WBRT 20 Gy in 5 fractions. The median survival of all patients was 2 months. There was no significant difference between BSC and WBRT 20 Gy; however WBRT 30 Gy had a marginally longer survival compared to BSC (2.2 vs 1.7 months, P = 0.002). Further subgroup analysis revealed that the difference in survival was limited to a patient with primary small-cell lung cancer.

Based on historical series data, it is a common assumption that WBRT improves survival compared to BSC. There has been only one randomized trial (Horton et al., 1971) (in the pre-CT era) comparing WBRT to BSC. Forty-eight patients with the presumptive diagnosis of BM were randomized to steroids with or without WBRT 40 Gy. The addition of WBRT improved survival (14 vs 10 weeks, P not reported) and duration of remission. More recently, the QUARTZ trial set out to answer this question.

The QUARTZ trial is a randomized, non-inferiority, phase III trial comparing optimal supportive care (OSC) alone to WBRT (20 Gy in 5 fractions), in patients with inoperable BM from non-small-cell lung cancer. The primary endpoint is improvement in quality-adjusted life years (QALY). This trial initially suffered poor accrual and the interim data was released (Langley et al. 2013). Fortunately, the trial met its target accrual and mature results were published (Mulvenna et al. 2016). Notably, about 40% of the patients had KPS <70, and 80% had GPA score of 2 or less. Median survival was not different between the 2 arms (49 vs 51 days, HR 1.06 95% CI 0.9–1.26). QALY was also not different (46.4 vs 41.7 days). Median dose of dexamethasone was also similar between both arms (8 mg). Subgroup analysis suggested that younger patients and patients with better performance status and controlled systemic disease may benefit from WBRT. One must note the characteristics of the

included patients – a sizeable proportion of the patients were of poor performance status and all were unsuitable for surgery or SRS. As such, in patients with poor prognosis, supportive care is not much worse than WBRT in terms of survival, QoL, or QALY.

As mentioned earlier, the use of SRS in poor PS patients is controversial. Sanghavi et al. (2001) published a large retrospective series (502 patients from 10 institutions) where both SRS and WBRT were used. Patients were stratified according to RPA, and survival was significantly different between groups (RPA 1 16.1 m vs RPA 2 10.3 m vs RPA III 8.7 m, $P < 0.001$). These results were significantly better compared to survival of historical cohorts treated with WBRT alone (7.1 vs 4.2 vs 2.3 m, $P < 0.05$). The conclusion from this study was that the survival benefit, from SRS, was not restricted to RPA class. However, one has to interpret this conclusion cautiously, as patient selection bias would have confounded the results of this retrospective series.

7.1 Asymptomatic Patients

The use of high-resolution fine-slice MRI technology has enabled us to detect BM prior to patients developing symptoms. The incidence of asymptomatic BM has been reported to be as high as 18% at diagnosis (Kim et al. 2005).

Most of the evidence in the management of asymptomatic BM comes from NSCLC. Kim et al. (2010) reported the outcome of 135 patients with newly diagnosed NSCLC and asymptomatic synchronous BM. Of these, 78 (57.8%) received upfront chemotherapy, 27 (20%) received WBRT followed by chemotherapy, and 24 (17.8%) received SRS followed by chemotherapy. There was no significant difference in OS among the three groups (13.9 vs 17.7 vs 22.4 m, $P = 0.86$). However, subgroup analysis of adenocarcinoma patients (110 patients) had significant survival gains with SRS (29.3 m) compared to WBRT (17.7 m, $P = 0.01$) or chemotherapy alone (14.6 m, $P = 0.04$). Of note, only about 11% of patients were treated with tyrosine kinase inhibitors, TKI (like gefitinib or erlotinib). This study did not report EGFR mutation status, and it is unclear if these results are applicable to that group.

This led to a phase III RCT (Lim et al. 2015) comparing SRS to observation in patients with asymptomatic BM (up to 4) from NSCLC. Unfortunately, the study closed early due to poor accrual. There were 49 patients in both arms, which was balanced for both GPA and EGFR mutation status (30%). There was no difference in OS between the SRS (14.6 m) and the observation group (15.3 m, $P = 0.418$). As expected, the intracranial local progression-free survival was prolonged in the SRS group (not reached vs 10.2 m, $P < 0.001$). Of interest, the overall response rate (ORR) in the upfront chemotherapy group was 37%. Although this study is underpowered, the lack of survival difference may also be attributed to the effective salvage therapy used in both groups.

8 What Is the Role of Systemic Therapy in Patients with BM?

Historically, systemic therapy has mainly been used as the upfront choice for highly chemosensitive malignancies (e.g., germ cell tumor, small-cell lung carcinoma). Emerging data from trials (such as the one above (Lim et al. 2015)) have offered the option for upfront chemotherapy in asymptomatic BM from NSCLC.

There are two main obstacles for the use of systemic therapy in BM: firstly, the intrinsic chemosensitivity of the lesion and, secondly, the blood-brain barrier permeability of the chemotherapy agent. Although BM cause variable amounts of blood-brain barrier breakdown, as evidenced by contrast enhancement on imaging, the concentration of these agents within the brain is unpredictable.

Conventional chemotherapy has not made much progress in phase III trials. For example, topotecan and carboplatin given in combination with WBRT failed to show a survival advantage over WBRT alone in patients with BM from NSCLC (Neuhaus et al. 2009; Guerrieri et al.

2004). Temozolomide and thalidomide for BM from melanoma failed to show any improvement (Krown et al. 2006).

However, targeted therapies (small-molecule inhibitors and monoclonal antibodies) have shown promise in the management of BM. When targeted agents are able to effectively control micrometastatic disease, the need for WBRT can potentially be obviated. For example, lapatinib has been shown to prevent new BM (Cameron et al. 2008) and is active against established BM (Lin et al. 2009; Bachelot et al. 2013). A meta-analysis by Soon et al. (Soon et al. 2015) indicates the response rate of tyrosine kinase inhibitors in EGFR-mutant patients with BM to be in the range of 83% (95% CI 76–91%). The use of dabrafenib (Long et al. 2012) and vemurafenib (Dummer et al. 2014) in BM from BRAF-mutant melanoma shows response rates ranging from 30% to 39%. However, sunitinib was reportedly ineffective against BM from renal cell carcinoma (Chevreau et al. 2014).

The combination of targeted therapy and radiation has been explored in many completed and ongoing trials. An early trial, which failed to accrue completely, was the RTOG 0320 trial (Sperduto et al. 2013). One hundred twenty-six patients with NSCLC primary and 1–3 BM were randomized into WBRT+ SRS, WBRT+ SRS + temozolomide, and WBRT + SRS + erlotinib. Temozolomide or erlotinib was offered in the adjuvant setting up to 6 months after the completion of radiation. The median survival between the groups was not significantly different likely due to the lack of power (13.4 m vs 6.3 m vs 6.1 m). Combination therapy has caused grade 3–5 toxicities to be significantly higher with systemic therapy.

Contrary to the findings of RTOG 0320, Welsh et al. (2013) found no significant added toxicity when erlotinib was added to WBRT in their single-arm phase II study. Moreover, the response rate was 86%, and patients had improved survival with combination therapy compared to historical controls.

The combination of SRS with targeted and immune systemic therapies has been increasingly utilized and reported. For instance, SRS has been combined with ipilimumab (anti-CTLA4) demonstrating to improve median survival from 4.9 to 21.3 m (Knisely et al. 2012). Anti-PD-1 agents with SRS have been shown to improve lesional response further, but its impact on survival is still unknown (Qian et al. 2016). For BRAF V600E-mutant patients, the combination of SRS and vemurafenib was potent with 75% patients responding and nearly half having a complete response (Narayana et al. 2013).

A comprehensive review of this topic is beyond the scope of this chapter. Although impressive response rates (mostly radiological) have been observed, further phase III trials are needed to see if this translates into improved survival as the only two phase III trials have failed to demonstrate any survival benefit with combination treatment (Sperduto et al. 2013; Lee et al. 2014). As radiation therapy is combined with targeted and immune systemic therapies that have shown activity in the brain, better synergy may be noted for improved survival benefit. However, increased toxicity may also be seen and combination treatment needs further study.

9 What Are the Ways to Mitigate WBRT Toxicity?

Investigators have spent much effort to evaluate methods that may reduce the long-term impact of WBRT, with particular attention to neurocognition and QoL.

Parallels were drawn between the pathophysiology of vascular dementia and changes seen post-WBRT. The vascular hypothesis of radiation damage implicates radiation-induced atherosclerosis and microangiopathy, which ultimately leads to small infarcts secondary to vascular insufficiency. The N-methyl-D-aspartate (NMDA) receptor is involved in learning and memory. Ischemia can induce excessive NMDA stimulation leading to excitotoxicity. It was hypothesized that agents that block the NMDA receptor may protect against further damage. Memantine, an NMDA receptor antagonist, was investigated in the RTOG 0614 trial (Brown et al. 2013). This double-blind, placebo-controlled

trial randomized 554 patients into WBRT (37.5 Gy in 15 fractions) with memantine (for 24 weeks) or placebo. Patients were assessed with a battery of neuropsychological tests including HVLT, COWA, and MMSE. The primary endpoint was preservation of cognitive function, particularly HVLT-R, at 24 weeks. Compliance on both arms was equally poor (only about 30% completed 24 weeks). Notably, only 149 were analyzed at 24 weeks as a majority had died (34%) and some withdrew consent (11%). There was a trend toward less decline in HVLT-R in the memantine arm (median decline of 0) compared to the placebo arm (median decline −0.9) at 24 weeks; however, this was not statistically significant (P = 0.059). Considering only 149 patients were available for analysis, this results in a mere 35% statistical power. Patients in the memantine arm had a longer time to cognitive decline (HR 0.78, 95% CI 0.62–0.99, P = 0.01) and lower probability of cognitive failure at 24 weeks (53.8 vs 64.9%).

Donepezil, a selective oral acetylcholinesterase inhibitor, increases acetylcholine signaling by slowing its synaptic degradation. Rapp et al. conducted a phase III placebo-controlled randomized trial (Rapp et al. 2015) investigating the role of donepezil (for 24 weeks) in patients who have undergone cranial irradiation. Overall, the composite scores did not vary between groups (P = 0.48). However, the donepezil group fared better in terms of memory, motor speed, and dexterity.

Besides pharmacology, the other approach to mitigate neurocognitive decline has been through hippocampal avoidance. Neural stem cells, located in the subgranular zone of the hippocampal dentate gyrus, have been associated with the formation of new memory. Radiation injury to these stem cells has been hypothesized to be the central cause of early cognitive decline. Hippocampal avoidance is a feasible strategy due to 2 reasons. Firstly, the incidence of perihippocampal BM has been reported to be low at 8.6%, based on retrospective data from 2 institutions involving 371 patients (Gondi et al. 2010a). Secondly, modern techniques, such as intensity-modulated radiotherapy, volumetric-modulated arc therapy, and helical tomotherapy, enable effective sparing of the subgranular zone of the hippocampus (Gondi et al. 2010b). This led to a single-arm phase II trial, RTOG 0933 (Gondi et al. 2014). This trial completed accrual faster than anticipated, despite the extensive credentialing required, suggesting the widespread interest to mitigate treatment-related toxicity. One hundred thirteen patients were treated with HA-WBRT 30 Gy in 10 fractions, and subjected to standardized cognitive function and QoL assessments. The primary endpoint was HVLT-R at 4 months. The mean relative decline in HVLT-R from baseline to 4 months was 7%, which was significantly lower than historical control ($P < 0.001$). These promising results have opened the door for ongoing phase III trials. For example, NRG CC001 is evaluating the combination of memantine to HA-WBRT. NRG CC003 is investigating the role of HA-WBRT for PCI in small-cell lung cancer.

10 How should We Treat Patients with Leptomeningeal Dissemination?

Leptomeningeal (LM) dissemination occurs in approximately 5% of patients with cancer. LM is more common with lymphoma, leukemia, breast cancer, lung cancer and melanoma. The overall prognosis is very poor, with the average survival being 4–6 weeks without therapy (Grossman and Krabak 1999). Few advances have been made in the treatment of LM in the past several decades. The goals of treatment in patients with LM are to improve QoL, by slowing or reversing the neurological deficits. Prolonged survival may be occasionally seen with endocrine-receptor positive breast cancer. Factors that influence treatment choice include performance status, presence of fixed neurological deficit and systemic tumor burden. Patients deemed to be of good prognosis, based on the multifocal nature of LM, may benefit from chemotherapy (intravenous, or intracerebrospinal fluid (CSF)). Best supportive care, with corticosteroids, and/or radiotherapy (to

symptomatic sites) is usually recommended for patients with poor performance status and multiple fixed neurological deficits.

10.1 Chemotherapy

The majority of the systemic agents fail to achieve cytotoxic concentrations within the CSF. Exceptions include high-dose intravenous methotrexate, cytarabine and thiotepa. However, toxicity stemming for high doses, and possible intrinsic resistance of underlying malignancy, limits the widespread use of these agents. Intra-CSF chemotherapy (via lumbar puncture or Ommaya reservoir) may be used to address the entire neural axis while having minimal systemic toxicity. The main agents which can be given intrathecally include methotrexate, thiotepa, cytarabine, and liposomal cytarabine. There is no strong evidence regarding the choice of these agents, except in lymphomatous neoplasms where liposomal preparation of cytarabine was shown to have a higher response rate and improved KPS (Glantz et al. 1999a). In solid malignancies, depot cytarabine has been shown to have a comparable response rate to methotrexate and increasing time to neurological progression (Glantz et al. 1999b). However, before the administration of intrathecal chemotherapy, one must ensure the patency of CSF flow (by radionuclide cisternogram). CSF blockage hampers the uniform distribution and may lead to increased neurotoxicity, secondary to pooling of chemotherapeutic agents. On occasion, limited-field radiotherapy may be utilized to overcome areas of CSF obstruction. Intrathecal targeted agents such as trastuzumab targeted at HER2neu + for patients with breast cancer may have more promising results though limited data currently (Zagouri et al. 2013).

10.2 Radiotherapy

Intrathecal chemotherapy is limited by its penetrability into deep tissue and thus has limited efficacy for nodular or bulky lesions. As such, external beam radiotherapy has a role in palliating symptomatic sites and areas of bulky LM disease. Cranio-spinal irradiation is used infrequently, due to the lack of survival benefit (Hermann et al. 2001) and significant acute toxicities (such as myelosuppression, odynophagia, mucositis, and nausea).

Classically, WBRT in the setting of LM covers the reflections of the meninges. Particular attention is paid to the cribriform plate, reflections along the optic nerve, inferior extent of temporal meninges, and exit regions of cranial nerves III, IV, V, and VI. Classic teaching recommends that the inferior edge of the field be at the C2/C3 junction; however, this does not stem from strong evidence. This likely originated in the pre-CT planning era, where prophylactic cranial irradiation was used for acute lymphoblastic leukemia (Krepler et al. 1975).

11 How Should We Prognosticate Patients with BM?

Forecasting the survival of patients forms the basis of decision-making and helps to streamline treatment recommendations. Patients who are expected to have a limited survival are unlikely to benefit from overly aggressive management. Unfortunately, doctors have been notoriously poor at prognostication. A prospective cohort study by Christakis et al. (Christakis and Lamont 2000) showed that merely 20% of doctors were accurate (within 33% of actual survival). The same study showed that most predictions (63%) were overestimates (usually by 5 times).

Karnofsky performance status (KPS) is often used as a yardstick, to estimate patient's prognosis. This is rightfully so, as KPS has emerged as a significant factor predicting survival on many prognostic indices. However, there can be significant inter-assessor variability when determining a patient's KPS. For example, Hutchinson et al. (1979) reported an inter-rater agreement of only 29%. However, this may have been spuriously low as this study was performed in the emergency room on hemodialysis patients. Sorensen et al.

(Sorensen et al. 1993) performed a single-center study, involving 100 consecutive cancer patients, assessing the reliability of the ECOG scale. Only moderate agreement was found between the 3 observers (Kappa 0.44 95% CI 0.38–0.51). Fortunately, agreement with regard to allocation of patient's PS 0–2 versus 3–4 was high.

More relevant to this chapter, Kondziolka et al. (2014) performed an interesting prospective study. Data of 150 consecutive cancer patients with BM undergoing SRS were recorded (including histology, number of BM, extracranial disease status, age, KPS). Eighteen cancer specialists (neurosurgeon, radiation oncology, medical oncology) were asked to prognosticate the survival of these patients. In patients who died within 10 months of SRS (median survival 4.2 months), the predictions of neurosurgeons (8.7 m), radiation oncologists (8.3 m), and medical oncologists (7 m) were all overoptimistic. Of the 2700 predictions, 1226 (45%) were off by more than 6 months and 488 (18%) were off by more than 12 months.

Many models have been developed to aid clinicians in prognosticating survival of this group of patients. The earliest of these was the recursive partitioning analysis (RPA) model (Gaspar et al. 1997). This was based on 1200 patients, entered into 3 consecutive RTOG trials, from 1979 to 1993. This statistical method, based on 18 pretreatment characteristics and 3 treatment-related variables, provided 3 classes. RPA class I patients (median survival 7.1 months) were less than 65 years, had a KPS of at least 70, and had controlled primary tumor with the brain-only metastasis. RPA class III patients (median survival 2.3 months) had a KPS less than 70. RPA class II (median survival 4.2 months) consisted of all other patients who did not fit into the other classes. The strengths of the RPA classification are that it has been validated in a prospective trial (Gaspar et al. 2000) and that it was easy to use in the clinics. However, it does come with several limitations. Firstly, the vast majority of these patients have unresectable and/or multiple metastases. Secondly, all the patients included in this analysis received WBRT, and therefore the effect of focal therapy is not reflected. Thirdly, the trials were conducted prior to the advent of effective imaging modalities and systemic therapy, affecting its generalizability to the modern era. Moreover, majority of patients would fall into class II, which tends to be heterogeneous and does not provide discriminatory power.

The RTOG 95-08 trial (Andrews et al. 2004) reported a survival benefit with additional SRS (to WBRT) for patients with solitary BM, but not for 2 or 3 BM. As such, number of BM was thought to be an important prognostic factor, based on that trial. Moreover, the RPA classification required an estimation of systemic disease control, which can be highly varied due to interpretation bias and imaging modalities used.

The graded prognostic assessment (GPA) model ($n = 1960$, including 328 from the RTOG 9508 trial) was conceived to include number of lesions, in addition to age, KPS, and extracranial disease (binary format) (Sperduto et al. 2008). The sum of each of these four factors (scored 0, 0.5, or 1) will be utilized to classify patients into four groups (0–1, 1.5–2.5, 3, 3.5–4). The respective median survival was 2.6 m, 3.8 m, 6.9 m, and 11 months ($P < 0.0001$).

However, owing to the heterogeneous nature of BM patients, there was still equipoise regarding the optimal treatment. Clearly, primary tumor histology influences the behavior of the secondary intracranial lesions and treatment response. A more recent model, through a multi-institutional effort involving 4259 patients, has been formulated (Sperduto et al. 2010, 2012). The diagnosis-specific GPA (DS-GPA) evaluated patient outcomes by diagnosis and treatment rendered and correlated the GPA scores by diagnosis. Prognostic factors for survival were determined for each primary site, and only statistically significant ones were used to determine the DS-GPA score. NSCLC patients form the majority (44.3%), followed by breast (15.1%) and melanoma (11.3%). Table 2 lists the prognostic factors (by diagnosis group) as well as the estimated median survival. Outcomes were also influenced by treatment rendered. For example, in NSCLC, all treatments were considered superior to WBRT alone; in breast cancer, WBRT + SRS/surgery, surgery + SRS, or a combination of these is

Table 2 Diagnosis-Specific GPA

GPA scoring criteria								Median survival (m)
	0	0.5	1	1.5	2	3	4	
Non-small cell and small-cell lung cancer								
Age(y)	>60	50–60	<50					GPA 0 – 1 = 3 GPA 1.5 – 2 = 5.5 GPA 2.5 – 3 = 9.4 GPA 3.5 – 4 = 14.8
KPS	>70	70–80	90–100					
ECM	Present	–	Absent					
No. of BM	>3	2–3	1					
Melanoma								
KPS	<70		70 – 80		90–100			GPA 0 – 1 = 3.4 GPA 1.5 – 2 = 4.7 GPA 2.5 – 3 = 8.8 GPA 3.5 – 4 = 13.2
No. of BM	>3		2–3		1			
Breast cancer								
KPS	<50	60	70–80	90–100				GPA 0 – 1 = 3.4 GPA 1.5 – 2 = 7.7 GPA 2.5 – 3 = 15.1 GPA 3.5 – 4 = 25.3
Subtype	Basal		Luminal A	Her-2	Luminal B			
Age(y)	>=60	<60						
Renal Cell Carcinoma								
KPS	<70		70 – 80		90–100			GPA 0 – 1 = 3.3 GPA 1.5 – 2 = 7.3 GPA 2.5 – 3 = 11.3 GPA 3.5 – 4 = 14.8
No. of BM	>3		2–3		1			
GI Cancers								
KPS	<70		70		80	90	100	GPA 0 – 1 = 3.1 GPA 2 = 4.4 GPA 3 = 6.9 GPA 4 = 13.5

superior to WBRT alone (however, SRS alone was not statistically superior to WBRT). This model provides a more granular assessment of patient outcome and helps to refine decision-making in the clinics. This colossal multi-institutional effort has to be lauded; however, one has to keep in mind that this is based on retrospective data which is prone to patient selection bias.

A nomogram for individualized estimation of survival based on 7 RTOG trials (n = 2367) (Barnholtz-Sloan et al. 2012). The rationale for this stemmed from the wide distribution of survival seen within each RPA class or DS-GPA score group. The nomogram provides survival estimates at median, 6 m and 12 m. Such a personalized tool is especially useful in the clinic for counselling patients on clinical outcomes and prognosis. However, this nomogram has yet to externally validated. Moreover, the data was derived from trials spanning many years (1979–2001), where effective systemic therapy and/or SRS may not have been utilized. As such, this may lead to an underestimate of survival of patients in the modern era.

12 Should We Consider the Cost-Effectiveness of Each Strategy?

Many policy makers and administrators have started to emphasize on value-based medicine. From a societal perspective, resources of spent on healthcare have to be seen in the context of quality-of-life years gained from a particular treatment. This is especially pertinent to patients with BM. A WBRT for-all strategy may be cheap and easy to implement, but the survival detriment (WBRT without surgery/SRS) in patients with limited BM has been categorically proven. SRS for patients with multiple BM will come under scrutiny, as there may be conflicts of interest stemming from the fee-for-service payment model. Furthermore, the costs incurred from the treatment and/or regular and frequent surveillance MRI, let alone salvage procedures, can be considerable. Do the benefits justify the costs? What is the threshold we are willing to pay for an additional of year of life? This may vary between countries and between perspectives (patient's perspective, payer's perspective, or societal perspective). Costs incurred may be indirect – i.e., additional time off-work or inability to be economically productive, increased care required, costs from frequent imaging, or costs from commuting to tertiary centers for healthcare. Comparing treatment cost alone, though this may vary widely, patients treated with SRS may be paying 2.2 more compared to those without (Halasz et al. 2013). Data from the 2008 non-Medicare charges indicate that a course of WBRT ranged from $9201 to 17,003; in contrast, SRS charges ranged from $40715 to 65,000 (Tsao et al. 2012c).

Cost-effective analysis (CEA) in the setting of BM has been very sparse. Research into this area is desperately needed, to form the basis of our fiscally prudent recommendations.

12.1 Surgical Resection vs SRS

Mehta et al. (1997) conducted a CEA comparing resection or SRS (with adjuvant WBRT), to WBRT alone for patients with single BM. Information was obtained from RCT, as well as multi-institutional retrospective data (1989–1994). Surgery was reported to be 1.8 times costlier than SRS. The SRS strategy was the most cost-effective: the average cost per week of survival being $310 for WBRT alone, $524 for surgery plus WBRT, and $270 for SRS plus WBRT. This study was one of the first evaluating cost-effectiveness in the context of radiation oncology. However, the cost derivation was from a retrospective review of single-institution billing data. Secondly, patient-related factors are likely to have been uncontrolled resulting in severe bias of outcomes, in favor of the surgery/SRS arms. Thirdly, the cost of follow-up and late complications was not considered for this study (presumably more in the surgery/SRS arms).

Similarly, Vuong et al. conducted 2 CEA comparing surgical resection to SRS (Vuong et al. 2012, 2013). One was based on a patient's perspective from a lower-income country (Vietnam), and the other based on the perspective from the German statutory health insurance system. In both settings, SRS was deemed to be more cost-effective than surgical resection.

12.2 SRS With or Without WBRT

The MD Anderson group performed a CEA (Lal et al. 2012), comparing SRS with or without adjuvant WBRT, from a healthcare institution perspective (based on the Chang trial (Chang et al. 2009)). The observation arm had a higher average cost ($119,000 compared to $74,000). This included costs from salvage therapy for recurrences, which was higher in this arm. However, as we know, the observation arm had a longer survival (1.64 life-years saved (LYS) versus 0.6 LYS). This equated to $41,783/QALY, for the observation arm. Even with sensitivity analysis, this strategy was more cost-effective, up to a willingness-to-pay threshold of $100,000/QALY.

Hall et al. conducted a CEA comparing SRS alone, SRS + WBRT, and surgery + SRS (Hall et al. 2014). Based on this retrospective study, there was no difference in OS (9.8, 7.4,

10.6 months). As before, the SRS alone required for salvage procedures. Despite that, the average cost per month of median survival favored the SRS alone strategy ($2412 (SRS), $3220 (SRS + WBRT), $4360 (surgery + SRS)).

Savitz et al. (2015) performed a base-case CEA comparing WBRT, SRS (with salvage), HA-WBRT, or a combination of these in a hypothetical cohort of patients (1–3 BM) expected to survive between 3 and 24 months. They reported that traditional treatments (WBRT, SRS alone) remained cost-effective for patients surviving between 3 and 6 months, whereas HA-WBRT and SRS + HA-WBRT became more cost-effective in longer survivors. This study demonstrates the cost-savings of mitigating late toxicity in potential long survivors.

It remains to be seen if SRS to multiple lesions (>4), compared to WBRT, is a cost-effective option and more studies are needed in this area.

13 What Is the Impact of Histology of Underlying BM?

Historically, majority of BM trials have not restricted participants to a specific primary tumor site. As a result, varying histologies have been placed into the same basket. These trials were understandably designed to maximize patient accrual. Moreover, WBRT doses were determined more by tolerance of normal brain parenchyma, rather than underlying histology. Typically, non-small-cell lung cancer patients make up to 50% of the trial participants, with the 2nd largest group either being breast cancer or melanoma.

Over the years, we are aware that the natural history of each disease is unique. Even within a particular histological group, there exists remarkable heterogeneity due to different molecular subtypes and their varying responsiveness to treatments. For example, a patient with a luminal B subtype breast cancer has a drastically improved prognosis compared to a patient with basal subtype (Sperduto et al. 2012). Moreover, the onslaught of targeted therapies has changed the landscape within the oncology clinic, especially for those with targetable driver mutations (e.g., gefitinib for EGFR-mutant lung cancer).

As such, we need to have a more granular assessment of patients presenting with BM. DS-GPA provides some evidence that the underlying histology influences prognosis (Sperduto et al. 2010). However, the heterogeneity of enrolled patients, and the lack of molecular subtypes, hampers the identification of prognostic factors.

As alluded to earlier, Nieder et al. (1997) have demonstrated the complete remission rates differed by underlying histology when WBRT was applied. Certain histological types are thought to be more "radioresistant" than others. The ECOG 6397 phase II trial (Manon et al. 2005) evaluated the utility of SRS alone in patients with 1–3 BM from renal cell carcinoma, melanoma, and sarcoma. These are traditionally thought to be more radioresistant. Doses were selected by tumor size and ranged from 15 to 24 Gy. The infield failure rate was 32.2%, at 6 months, which is relatively higher than other series (Flickinger et al. 1994). Chang et al. (2005) reported a retrospective series (n = 189) over a 10-year period. The 1-year freedom from progression was 64% for renal cell carcinoma, but much lower for melanoma (47%) and sarcoma (0%) patients.

Moving forward, we will need to design clinical trials with an enriched cohort of patients from selected histological groups, where molecular subtyping and driver mutation status is available. This will allow us to elucidate the true impact of BM-directed treatment for that particular histology.

14 Response Assessment and Follow-Up

There can be substantial variation in the interpretation of response for a patient with BM. Factors contributing to this variation include modality and frequency of assessment, the magnitude of change, and (lack of) ability to differentiate between tumor-related and treatment-related changes. Furthermore, patients treated with SRS

Table 3 Summary of recommendations by RANO-BM group

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but >20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease
New lesion(s)[a]	None	None	None	Present
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable[b]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse
Requirement for response	All	All	All	Any of the above

[a]A new lesion is one that is not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. For immunotherapy-based approaches, new lesions alone do not define progression

[b]Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

or immunotherapy may experience pseudoprogression. Recently, the Response Assessment in Neuro-oncology Brain Metastases (RANO-BM) working group published their proposal (Lin et al. 2015). A summary of their recommendations are presented in Table 3.

For patients treated off-trial, especially with a SRS alone approach, regular and frequent imaging schedule should be followed. Although no guidelines exist, most practitioners obtain surveillance imaging every 3 months. As such, the physician and patient must ascertain that resources are available prior to adopting this strategy.

Conclusion

Few topics in radiation oncology have stirred more controversy and debate than the management of BM and the role of SRS and WBRT. Deeply etched opinions have influenced clinical practice, which at times cannot be justified based on the limited level 1 evidence. Neurocognitive detriment, which has been notoriously (and sometimes unfairly) linked to WBRT, has caused a paradigm shift within the oncology community.

Consistently, multiple RCTs have demonstrated reduced local and distant intracranial failure with WBRT, but no survival benefit (likely due to early and effective salvage) and decline in NCF and QoL. Subgroup or post hoc analyses have demonstrated a survival benefit (for SRS + WBRT) in certain groups, but these need further validation. Many cooperative groups have shifted their focus from prolonging survival to maintaining patient's physical and mental function, for as long as possible, as their primary goal.

SRS and WBRT should be viewed as complementary, rather than competition. It seems reasonable to offer SRS alone, with close surveillance, in high-functioning patients who are concerned about cognitive decline. In patients deemed to have a high risk of distant intracranial failure, adjuvant WBRT may be used sparingly. With the available technology, many have combined the best of both worlds with hippocampal-sparing WBRT with simultaneous integrated boost techniques (Bauman et al. 2007; Gutierrez et al. 2007; Hsu et al. 2010).

Effective targeted systemic agents continue to be evaluated, which tackle both intra- and extracranial disease, and may reduce the standing of radiation and surgery. Future research should be conducted in an enriched cohort of patients,

which should be histology-specific groups and include molecular subtyping (e.g., RTOG 1119). Cost-effectiveness outcomes should be integrated into these randomized trials.

Until that evidence is clear, we should align with the Hippocratic Oath of "primum non nocere."

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Controversies in the Management of Solid Tumor Bone Metastases

Andrew M. Farach, E. Brian Butler, and Bin S. Teh

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Abstract

Bone metastases from solid tumor origin are challenging to manage and require a coordinated multi-specialist effort. Skeletal related events result in a significant societal burden and the predominant goal of the orthopedic oncologist is palliation of pain and preservation of function. Given the wide range of clinical scenarios that may be encountered, controversies exist both within and among specialties. This chapter reviews the current landscape in the management of bone metastases with a focus on commonly encountered sub-sites including long bones, spine, and periacetabular metastases.

1 Introduction

Bone metastases are commonly encountered in patients with advanced solid tumors. The most common primary sites are breast, prostate, and lung cancer, followed by kidney and gastrointestinal primaries. Skeletal related events (SRE) can result in substantial morbidity including pain, pathological fractures, spinal cord compression, nerve root compression, and hypercalcemia (Wilkinson et al. 2008). The prevalence of patients with solid tumors and bone metastases exceeded 330,000 in 2012 and is expected to increase with improved systemic therapies (Hernandez et al. 2015). Patients experiencing an SRE are more likely to develop a subsequent

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SRE, have poorer survival, have decreased quality of life, and require more health resources (Hernandez et al. 2018). A multidisciplinary team is required to manage bone metastases and necessitates a coordinated effort between medical oncologists, surgeons, radiation oncologists, interventionalists, and rehab professionals. Given the evolving strategies in systemic management and local therapies for bone metastases, many controversies exist. This chapter reviews the current landscape in the management of bone metastases.

2 Medical Management of Bone Metastases

Medical management of bone metastases is important as 40% of patients will develop an SRE without intervention (Gravalos et al. 2016). As tumor cells metastasize to bone, important homeostatic properties of osteoblasts and osteoclasts are disrupted which can result in enhanced tumor growth. One key promoter of osteoclast differentiation and activation is RANK-Ligand (RANKL).

2.1 Bisphosphonates

Zoledronic acid (ZA) is a third-generation bisphosphonate and the most effective in preventing SREs. ZA reduces SREs for solid tumors (except castrate-sensitive prostate cancer) and significantly delays the median time to first SRE (Rosen et al. 2004; Kohno et al. 2005; Saad et al. 2004). Given that no trial has demonstrated a survival benefit to ZA, it is considered a palliative therapy. Administration is 4 mg intravenous infusion every 3–5 weeks at the first detection of bone metastasis with recent evidence suggesting that every 12-week administration is non-inferior (Hortobayi et al. 2014; Himelstein et al. 2015). Candidates for ZA should have a >3-month life expectancy and a serum creatinine <3.0 mg/dL (Breast Cancer NCCN Evidence Blocks 2018). As there is a risk of osteonecrosis of the jaw, a dental exam is recommended prior to initiation of therapy. Acute-phase responses may occur after ZA administration and are characterized by body aches, elevated temperature, and flu-like symptoms. Bisphosphonates are also effective in the treatment of hypercalcemia.

2.2 RANKL Inhibitors

Denosumab is a human monoclonal antibody which binds to and inhibits RANKL. Denosumab is superior to ZA in delaying and preventing SRE in solid tumors and has also been shown to prevent pain progression (Stopeck et al. 2010; Fizazi et al. 2011; Scagliotti et al. 2012a; Henry et al. 2014). It was initially approved by the FDA in late 2010 for the prevention of SREs. Administration is 120 mg subcutaneous injection every 4 weeks. No survival benefit has been demonstrated for denosumab; however, a subset analysis of NSCLC patients had improved median overall survival (OS) compared to those treated with ZA, with the benefit limited to patients with squamous histology (Scagliotti et al. 2012b). Denosumab carries a similar risk of osteonecrosis of the jaw to that of ZA and similar recommendations exist regarding prophylactic dentistry. Denosumab also carries a risk of hypocalcemia and unlike ZA requires no renal monitoring.

2.3 Vitamin D and Calcium

Both ZA and denosumab should be administered in conjunction with supplemental calcium 1200–1500 mg and vitamin D_3 400 to 800 IU daily.

2.4 Medical Management in Combination with Radiation Therapy

It appears that bisphosphonates and denosumab are safe to administer concurrently with external beam radiation therapy (EBRT) (Choudhury et al. 2011; Yamada et al. 2012). While bisphosphonates are not thought to replace EBRT for painful bone metastases, recent evidence suggests some efficacy in

providing pain relief. A comparative trial of EBRT or ibandronate demonstrated equal pain relief at 4 and 12 weeks but more rapid relief in the EBRT arm. Given only short-term follow-up in this study, bisphosphonates were noted to be a consideration for pain relief when EBRT is not available (Hoskin et al. 2015).

3 Radiation Dose Fractionation, the Debate Continues

For previously unirradiated, painful bone metastases, several dose fractionation schedules exist. In fact, in a review by CMS, over 100 dose fractionation strategies have been utilized in this diagnosis. The most common of which are 8 Gy in a single fraction, 20 Gy in five fractions, 24 Gy in six fractions, or 30 Gy in ten fractions. Stereotactic ablative techniques are also employed in select cases; however, this will be discussed later in the chapter. These standard regimens carry overall response rates of 60–80% in various series as defined by reduction in pain scores or opioid use. Complete response is seen in roughly 25% of cases. Several randomized, non-inferiority trials comparing single-fraction (SF) and multiple-fraction (MF) regimens conclude that SF is non-inferior to MF with regard to pain control and toxicity (Lutz et al. 2017). In patients with longer life expectancy, retreatment rates are 2.6-fold higher for SF versus MF therapy, which may impact decision-making (Chow et al. 2012).

Given an expanded focus on cost containment and quality in healthcare delivery, it is important to consider the cost-effectiveness of various strategies for palliation of bone metastases. According to one analysis for men with hormone-refractory prostate cancer, SF radiation was the most cost-effective strategy and was more cost effective than MF strategies (Konski 2004). Pain medication was the cheapest approach but carried poor quality-adjusted survival, while chemotherapy was the most expensive and carried the poorest quality-adjusted survival. In a Dutch trial, which accounted for increased retreatment in the SF cohort, only an 8% cost difference was noted, with the most significant economic advantage being increased radiotherapy capacity (Steenland et al. 1999). In resource-rich countries such as the United States with ample radiotherapy capacity, this advantage is likely of limited significance.

Despite the above data, MF regimens often are favored over SF regimens in the United States. In a review of the National Cancer Database (NCDB) assessing trends in fractionation schedule from 2005 to 2011 for non-spinal lesions, SF utilization was low but increased from 3.4% to 7.5% over the study period (Rutter et al. 2015). In this study, predictors of SF treatment were older age, further distance to travel for therapy, treatment at an academic facility, and non-private health insurance. Even in academic institutions, only 10.1% of patients received SF therapy in 2011. Rates of SF utilization are significantly higher in the United Kingdom and Canada, ranging from 30% to 65% in various series (Rutter et al. 2015). One plausible explanation for this discrepancy is the fee-for-service payment model in the United States; however, other plausible explanations exist. In an effort to increase utilization of SF therapy, the American Society for Therapeutic Radiology and Oncology (ASTRO) initiated the Choosing Wisely campaign stating that "strong consideration should be given to a single 8 Gy fraction for patients with a limited prognosis or with transportation difficulties" (Choosing Wisely, American Society for Radiation Oncology (ASTRO) 2015).

Even in countries with higher utilization of SF therapy, questions persist regarding underutilization given the data for non-inferiority of SF therapy. In surveys of preferred fractionation schemes for Australian and New Zealand radiation oncologists, the majority of physicians favored fractionation (Roos 2000). The most commonly cited indications for fractionation were desire to minimize recurrent pain, influence of training, desire to minimize risk of neurological progression, and desire to optimize tumor regression. In this study, poor performance status was the biggest driver of SF treatment; however, the presence of neurological signs/symptoms prompted fractionation.

So what drives the selection of fractionation over SF therapy? Despite the evidence for SF therapy, there remains doubt with regard to the scope of its utilization in clinical practice. This is

even inherent in the Choose Wisely recommendation, limiting the recommendation to patients with limited prognosis or transportation difficulty. Within this recommendation is an unstated assertion that MF may be favorable in patients with better prognosis or a short commute. One explanation is the understanding of selection bias in randomized controlled trials. In fact, a majority of comparative trials examining fractionation in bone metastases exclude patients with impending/existing pathological fracture, spinal cord compression, cauda equina compression, or previous radiation (Cheon et al. 2015). Therefore, recommendations for SF treatment may be limited to subsets of patients encountered in daily clinical practice. What is missing from the ASTRO and American College of Radiology (ACR) guidelines for the treatment of bone metastases is a measure of patient selection. It is important to distinguish "complicated" from "uncomplicated" bone metastases as it relates to fractionation recommendations. In current clinical training, this concept is not explicitly defined or tested.

Cheon et al. have proposed a definition of "uncomplicated" bone metastases as those unassociated with impending or associated pathological fracture, spinal cord compression, or cauda equina compression (Cheon et al. 2015). While there may be a range of definitions for impending fracture or spinal cord compression, there is a benefit to the simplicity of this definition. The Centers for Medicare & Medicaid Services (CMS) has a hospital outpatient quality reporting program (OP-33) to assess the percentage of patients with a diagnosis of painful bone metastases who receive radiation therapy with acceptable fractionation. The CMS exclusion criteria for "uncomplicated" bone metastases include previous radiation to the same site, spinal cord compression, radicular pain at the site of bone metastasis, participation in a clinical protocol involving radiation, surgical stabilization of the site, or femoral axis involvement >3 cm (Hospital Outpatient Quality Reporting Program 2016). Based on these definitions, we propose the following definition of "complicated" bone metastases where multidisciplinary management, MF techniques, or stereotactic ablative regimens may be most appropriate (Table 1).

Table 1 Complicated solid tumor bone metastasis

• Previous irradiation to site
• Extensive soft-tissue component
• Impending/associated pathological fracture (consider Mirels, SINS scores)
• Femoral axis involvement >3 cm
• Surgical stabilization
• Spinal cord compression
• Cauda equina compression
• Radicular/neuropathic pain
• Radioresistant histology

4 Multidisciplinary Management of Spine Metastases

The spinal column accounts for 13% of the skeleton (Johnson 2018). Despite this, the spine is the most common site of bone metastasis. Spine metastases may be the most complex site to manage given the intimate association with neurological structures and various modalities available for treatment. As treatment of spine metastasis is almost exclusively palliative in nature, the goal of therapy is to preserve or restore neurologic function, improve quality of life, and maintain stability while establishing durable local control. Malignant spinal cord compression (MSCC) complicates the picture as it occurs in up to 20% of patients with spine metastases and can result in significant morbidity and reduction in quality of life. Various scoring systems and algorithmic approaches have been developed to aid in medical decision-making.

4.1 Scoring Systems

MSCC represents an oncologic emergency. For patients presenting with MSCC, the classic Patchell trial established surgery and postoperative radiation therapy as the standard for patients with paralysis <2 days (Patchell et al. 2005). This trial oversimplifies decision-making as patients with similar disease presentation in the spine

may have vastly different prognosis, performance status, or ability to tolerate multimodal therapy.

As many practicing radiation oncologists' experience suggests, the Patchell study underestimated the efficacy of EBRT in the management of MSCC. The Rades scoring system was developed in 2008 to better predict ambulatory outcomes for patients treated with conventional radiation alone. This system incorporates tumor histology, interval since initial cancer diagnosis, presence of visceral metastasis, motor function, and time to motor deficit (Rades et al. 2008a). This data was based on outcomes in over 2000 patients. Patients with a score of ≥38 experienced post-RT ambulatory rates of 98% and suggest that EBRT alone is appropriate, whereas patients with scores ≤28 experienced post-RT ambulatory rates of 6% and were unlikely to experience any significant benefit to aggressive therapy. In these patients, short-course RT for pain or supportive therapy alone is likely more appropriate. For patients with intermediate scores, combination therapy with laminectomy and stabilization plus EBRT is recommended. This recommendation was validated in prospective fashion in 2011 (Rades et al. 2011). While this system helped to define treatment options for patients with MSCC, management remained unclear for many patients with epidural tumor extension but without frank MSCC.

The NOMS (neurologic, oncologic, mechanical, and systemic) decision framework was proposed by the Memorial Sloan Kettering group in 2013. This system seeks to accomplish effective palliation of spine disease while minimizing morbidity. Briefly, the neurologic component "N" is based on a scoring system validated by the Spine Oncology Study Group (SOSG) and utilizes axial T2-weighted MRI to determine the degree of epidural or spinal cord abutment. The oncologic component "O" is based primarily on tumor radiosensitivity to conventional EBRT (cEBRT). For patients with hematologic spinal tumors, cEBRT is almost universally recommended given the exquisite radiosensitivity of this disease. For solid tumors, radiosensitivity varies. More sensitive tumors (e.g., breast, lung, prostate) may be treated with cEBRT whereas more radioresistant tumors (e.g., lung, sarcoma, and melanoma) may require more ablative stereotactic (SRS/SBRT) regimen. According to this methodology, patients with grade 0-1b compression by MRI and radioresistant tumors are appropriate for cEBRT without decompression while patients with more significant compression may require multimodal therapy. Despite this recommendation, high-dose radiosurgery (24 Gy in a single fraction) has shown local recurrence of only 3% at 3 years irrespective of tumor histology, indicating that radioresistance can be overcome with ablative techniques (Yamada et al. 2011). Interestingly, the spinal cord must be limited at 14 Gy max dose (Yamada et al. 2008); however, local control is diminished with planning target volume doses less than 15 Gy (Lovelock et al. 2010). Given this tight dosimetric discrepancy, the concept of separation surgery was introduced to allow a minimum of 2 mm between cord and tumor to maximize local control.

Within the NOMS framework, mechanical instability "M" supersedes neurologic or oncologic recommendations as radiation therapy has no impact on spine stability and may in effect result in decreased stability with tumor response. In the setting of instability, surgical stabilization or percutaneous cement augmentation is recommended. Instability can be difficult to assess, especially for practitioners without formal orthopedic training. For this reason, the SOSG developed the Spinal Instability Neoplastic Score (SINS) to aid in assessing stability throughout the spine (Fisher et al. 2010). By assessing location, pain, bone lesion characterization, spinal alignment, collapse, and posterolateral involvement, a score is generated with stable, intermediate, and unstable classification to aid in decision-making. A validation study of this system demonstrated excellent inter- and intra-observer reliability regardless of specialty training (Fourney et al. 2011). After completion of stability assessment and taking into account neurologic and oncologic components, the most appropriate management is determined from a disease perspective.

Finally, the systemic assessment "S" takes into account comorbidities, metastatic tumor burden, and overall health status to determine if the patient will tolerate the suggested intervention with acceptable risk. While there are scoring systems to prognosticate survival in the setting of spine metastasis, systemic therapy continues to evolve with increasing targeted therapy and immunotherapy impacting survival. For this reason, the systemic assessment is individualized within the NOMS framework.

One such prognostic scoring system is the Tokuhashi scoring system established in 1989 and was revised in 2005. In this system, a predicted survival of <6 months prompts conservative treatment, i.e., cEBRT, while a predicted survival >1 year prompts surgical excision (Tokuhashi et al. 2005). Many other systems are utilized including the Tomita, Rades, modified Bauer, and Oswestry Spinal Risk Index (OSRI) (Tomita et al. 2001; Rades et al. 2008b; Leithner et al. 2008; Balain et al. 2013). A recent review found the Bauer and Oswestry index to carry the most accurate prognostic predictive ability (Cassidy et al. 2018). The OSRI is a very simple system taking into account primary tumor growth rate and general condition (Balain et al. 2013). In this system, lung cancer is defined as displaying "very rapid growth" and breast cancer is defined as "slow growth." While this system is externally validated, it maintains the same limitation as other scoring systems. As anticancer therapy evolves and we enter the era of molecular oncology, tumor biology can differ dramatically from one patient with lung cancer to another. Two patients presenting with the exact same spinal metastasis, one with a targetable EGFR mutation and the other with a squamous cell cancer, carry a dramatically different prognosis, and the same for a metaplastic triple-negative breast cancer versus a HER-2-positive metastasis. For this reason, these scoring systems should be considered in the context of available systemic therapies.

A consistent criticism of the aforementioned spine assessment strategies is the emphasis on intervention as the first thought. For this reason, the Medical/Mental, Oncologic, Stenosis, Stability (MOSS) patient-centered approach was developed (Marco 2018). This systems has similar components to NOMS but places the primary emphasis on identifying the patient's medical and mental reserve, "M." In this system, the onus is on the surgeon to thoroughly evaluate the ECOG performance status, nutritional status, mental status, extent of prior therapy, degree of debility, and social support structure to determine if the patient is a candidate for stabilization prior to evaluating the most appropriate intervention. Only in patients deemed fit to undergo such surgery should one proceed to evaluation of appropriate intervention. If the patient is a candidate for intervention, the next component is to assess the oncologic framework "O" of the case. This requires a good understanding of oncologic principles and alternative treatment options. An assessment of primary tumor histology, relative radiosensitivity, chemosensitivity, and life expectancy will help to avoid overly aggressive surgery and favor noninvasive approaches more frequently. Finally, stenosis "S" and stability "S" are assessed to determine if surgical intervention is warranted and if so what technique may be employed.

It is clear from this discussion that a multidisciplinary approach is necessary for assessment of the patient with MSCC. While each of the above scoring systems aids in decision-making and provides a framework to organize treatment algorithms, the central theme to these scoring systems is that multidisciplinary teams should develop a regimented approach to the management of patient with MSCC. Through a regimented approach, appropriate therapy can be individualized to the patient, as no two MSCC cases are alike.

4.2 Surgical Techniques

4.2.1 Vertebral Augmentation with Cement

Vertebroplasty and kyphoplasty are relatively new techniques for painful spinal compression fractures. Kyphoplasty is similar to vertebroplasty with the exception that in kyphoplasty a percutaneous balloon is inflated in the vertebral body to develop a cavity in the bone where cement can be injected. Multiple retrospective

and anecdotal reports support the efficacy of this technique near instantaneous pain relief or reduction. The Cancer Patient Fracture Evaluation (CAFÉ) study was a prospective, randomized trial for patients with 1–3 painful vertebral compression fractures. The primary endpoint was measured by improvement in Roland-Morris disability questionnaire (RDQ) at 1 month. In this study, treated patients noted significant improvement in RDQ −8.4 points compared to no significant change noted in the nonsurgical management arm (Berenson et al. 2011).

As vertebral cement augmentation (VCA) has little or no antitumor activity, it is often necessary to combine this technique with EBRT or another ablative approach. Debate exists, however, on the most appropriate sequencing. Various arguments can be made for or against each sequence. For instance, patients with instability may benefit immediately from VCA and this would be indicated under NOMS. Alternatively, for patients with stable compression fractures, pain relief may be achieved with cEBRT alone and VCA may be unnecessary and duplicative. In addition, VCA is associated with significant CT artifact and may limit subsequent tumor visualization. This can impede focused radiation therapy planning and would favor postradiation VCA, especially if more targeted stereotactic techniques are to be considered. There may also be concerns for tumor seeding or bleeding/infectious complications in patients receiving VCA prior to radiation therapy that could ultimately delay initiation of antitumor therapy. While VCA and EBRT may be complementary, further research is needed to assess the appropriate sequencing of these procedures.

4.2.2 Minimally Invasive Spine Surgery

Surgical resection of spine metastases can include en bloc removal of the tumor, piecemeal debulking, or palliative partial resection to relieve cord compression. Several techniques exist to achieve these varying degrees of resection and stabilization and include ventral, dorsal, and combined approaches. Determination of approach is typically made based on patient performance status and extent of disease with more aggressive approaches being limited to younger, healthier patients with limited disease burden. One major point of controversy relates to the use of minimally invasive surgery (MIS) over open surgery. Some reported benefits of MIS are reduction in muscular trauma, blood loss, pain, and length of hospitalization (Hansen-Algenstaedt et al. 2017a). MIS also includes various surgical techniques including percutaneous stabilization, "keyhole" spine surgery with a tubular retractor, mini-open procedures, and thoracoscopic/endoscopic procedures (Zuckerman et al. 2016). Due to a dearth of evidence, consensus is lacking and treatment approaches are left to the discretion and expertise of the physician.

Recently, a non-randomized, propensity-matched prospective trial compared outcomes of MIS and open surgery. Of 110 patients enrolled in this study, 80 underwent MIS and 30 open surgery. For the analysis, 30 patients undergoing MIS were matched to the 30 open cases in an attempt to diminish the effect of patient selection on the analysis. Tomita and Tokuhashi scores were included in the match in addition to other demographic and comorbidity parameters. The authors concluded that both MIS and open surgery resulted in improvements in performance status, pain, and neurological status. Open surgery, however, resulted in increased blood loss and transfusions and significantly longer hospitalization while MIS increased length of instrumentation and fluoroscopic time (Hansen-Algenstaedt et al. 2017b).

4.3 Stereotactic Radiation Therapy

Spine radiosurgery is an emerging approach for patients with spinal metastases. While conventional approaches are effective, dose is limited by relatively low radiation tolerance of the spinal cord and cauda equina. Advancements in radiotherapy planning and image guidance have allowed for more precise delivery of therapy and allow for dose escalation. Spine radiosurgery is also a relatively convenient outpatient procedure, requiring only 1–5 treatment sessions. Reported advantages of spine radiosurgery are shown in Table 2 (Harel and Angelov

Table 2 Advantages of spine radiosurgery

• Noninvasive, no recovery time
• Rapid pain improvement
• Improved local control rates
• Improved efficacy for radioresistant tumors
• Allows for re-irradiation after conventional RT
• May allow for decreased surgery
• May decrease dose to normal tissues (spinal cord, bone marrow, bowel, skin, etc.)
• Minimizes delays in systemic therapy
• Potentially curative in oligometastatic state

2010). While spine radiosurgery may provide a potential advantage over conventional techniques, it requires expertise that may not be available outside of academic centers and without specialized equipment. In expert hands, long-term pain improvement was noted to be dramatically increased over cEBRT series with 86% of patients experiencing long-term pain relief. Tumor control rates are also dramatically increased and up to 90% in patients treated with primary radiosurgery and 88% in those requiring salvage after previous cEBRT. In addition, 84% of patients with progressive neurological deficit noted at least some clinical improvement (Gerszten et al. 2007).

Given its efficacy, spine radiosurgery has shifted the treatment paradigm for patients with spine metastasis, namely MSCC. With local control in excess of 90%, the role of surgery is primarily to allow for adequate radiosurgery dosing (i.e., provide 2 mm separation of tumor from the spinal cord) and to achieve appropriate spinal stability. The concept of separation surgery was introduced and is now supported by the SOSG (Bilsky et al. 2005). Although the strength of evidence was determined to be low and based primarily on retrospective institutional experience, the strength of the recommendation was strong for combined separation surgery followed by radiosurgery. This so-called hybrid therapy results in decreased morbidity as compared to open surgery such as vertebrectomy and given the relative frailty of this patient group has become the standard of care in centers able to deliver high-quality spine radiosurgery. Patient-reported outcome data supports the use of hybrid therapy to decrease spine-specific pain severity and interference with general activity (Barzilai et al. 2018).

Of further interest, increasing evidence suggests that aggressive local therapies may extend survival for patients presenting in the oligometastatic state. While the definition of oligometastasis varies, a common definition allows for up to five metastatic lesions but limited to one or two organ sites. For patients presenting with oligometastasis involving the spine, radiosurgery may improve outcomes even in asymptomatic patients as an ablative procedure. In this concept, radiosurgery is utilized as an adjunct to systemic therapy to render the patient free of disease. This approach may be most useful in patients demonstrating a favorable initial response to systemic therapy. A recent international, multicenter, prospective study included patients with spine oligometastasis treated with surgical intervention or radiotherapy. Interestingly, treated patients with oligometastatic disease had improved survival at 3 and 6 months compared to those with polymetastatic disease (Barzilai et al. 2019). While the benefit of aggressive ablative therapy has yet to be confirmed in a phase III clinical trial, sufficient evidence exists to support formal investigation of this approach in randomized fashion.

5 Multidisciplinary Management of Long-Bone Metastases

Metastases of long bones also require multidisciplinary management and can present numerous management challenges that may differ from those seen in the spine.

5.1 Surgery

Surgery plays an integral role in the management of long-bone metastases. The primary goal of surgical management is to stabilize and prevent fracture or treat an existing pathologic fracture.

In fact, a systematic review was performed to evaluate the pain relief and functional outcomes as well as morbidity associated with surgical management of bone metastasis. In this review, 45 studies were included with results of 807 patients analyzed. Pain relief was demonstrated in 93% of cases and improved function noted in 89–94% of surgically managed long-bone metastases (Wood et al. 2014). Given these dramatic results, patients with long-bone metastases should be evaluated by an orthopedic oncologist, if available, or an orthopedist with oncologic experience to determine if surgical intervention is indicated. This recommendation was established in 1989 by Dr. Hilton Mirels in his seminal paper.

In this study, Mirels retrospectively reviewed 78 lesions that were irradiated without prophylactic surgical fixation. In 27 out of 78 lesions fractured within 6 months, fracture risk was predictable to blind observers based on pretreatment radiographs using the Mirels scoring system (Mirels 1989). One to three points are awarded based on tumor site (upper limb, lower limb, peritrochanteric), degree of pain (mild, moderate, functional), lesion (blastic, mixed, lytic), and size (less than one-third, one-third to two-thirds, and greater than two-thirds the bone diameter). A score of eight or higher suggests prophylactic fixation. Prophylactic fixation is preferred fixation of an existing fracture as it decreases operative time, is less morbid, and results in more rapid return to function.

The method of fixation differs primarily on the location of the lesion. For lesions of the proximal humerus an endoprosthesis is recommended, while a lesion involving the diaphysis may be treated with an intramedullary nail, less commonly resection and intercalary spacer, or even less frequently plates and screws. In lesions of the distal humerus flexible nails or elbow replacement surgery may be employed. In the femur, peritrochanteric lesions typically require an intramedullary nail while femoral neck and head lesions require hemiarthroplasty. Finally, in inoperable patients presenting with pathologic fracture or patients with limited life expectancy, external bracing may be most appropriate.

5.2 External Radiation Therapy

As previously discussed, multiple appropriate regimens exist for patients with long-bone metastases. For patients with uncomplicated lesions of the long bones and low Mirels score, SF EBRT or short-course MF regimens may be most appropriate as there are typically few nearby organs at risk. Typically a simple two-field technique is appropriate with effort made to spare a strip of skin to maintain lymphatic drainage of the extremity. Higher energy photons may allow for increased skin sparing and optimized Compton effect. For patients with complicated higher Mirels score, MF regimens may reduce the risk of fracture over SF EBRT if prophylactic fixation is not planned (Chow et al. 2014). In patients undergoing surgical fixation, the ACR appropriateness criteria supports 30 Gy in ten fractions as the primary fractionation regimen, although hypofractionated courses may be appropriate for select patients (Expert Panel on Radiation Oncology-Bone Metastases et al. 2012).

6 Multidisciplinary Management of Pelvic and Periacetabular Metastases

Metastases involving the periacetabular area carry significant morbidity due to pain and reduced mobility. As this is a load-bearing area, radiotherapy is effective in improving pain in the majority of cases; however, it does not modify the load capacity of the joint. Surgery in this area, including joint reconstruction and tumor resection, carries significant complication rates. Osteolytic lesions in this region pose significant fracture risk with resultant functional impairment (Muller and Capanna 2015).

6.1 Surgery

As the primary goal of surgery in this area is to address joint stability, anatomy is important. The

Table 3 Classification of pelvic bone metastases

Class	Characteristic
1	• Solitary metastasis • Good prognosis • >3 years since initial diagnosis
2	• Pathological fracture in zone 2
3	• Osteolytic lesion in zone 2
4	• Osteoblastic lesions involving multiple zones • Osteolytic or mixed lesions in zone 1 and/or 3 • Small zone 2 osteolytic lesion

Enneking classification divides the pelvis into four zones, with zones 1 (ilium) and 3 (ischium and pubis) representing non-weight-bearing or expendable bones, and zone 2 representing the periacetabular region with articulation of the femur. Zone 4 represents the sacrum (Enneking et al. 1990). Campanna and Campanacci proposed an algorithm using these zones combined with a classification to guide surgical management in pelvis.

According to this system (Capanna and Campanacci 2001) (Table 3), patients falling into classes 1–3 should be referred for evaluation by an orthopedic oncologist for surgical consideration:

If the patient is determined to be a surgical candidate, the surgical approach is the next consideration. The Harrington Classification was developed as a tool to guide surgical management (Harrington 1981). Briefly, Harrington 1 lesions have minimal effect on the acetabular structure and may be treated with simple curettage and cementing without total hip replacement (THR), and Harrington 2 lesions involve the medial wall of the acetabulum with an intact roof and lateral wall. In this case, a reinforcement ring with THR is necessary to avoid medial migration and loosening of a conventional hip prosthesis. Harrington 3 lesions have extensive osteolysis of the medial, lateral, and acetabular roof and require reconstruction using an implant and cement with the addition of stabilizing threaded pins in the surrounding hemipelvis and THR to shift load away from the joint. Harrington 4 lesions have complete acetabular collapse and require wide resection with reconstruction and THR.

In appropriately selected patients, surgical management of periacetabular metastases can improve patient performance status and quality of life (Ji et al. 2011), and potentially survival in the oligometastatic setting. Care should be taken to incorporate the expertise of orthopedic oncologists in the management of disease while considering other noninvasive approaches, patient performance status, and extent of disease in the pelvis and other visceral organ sites.

6.2 External Beam Radiation Therapy

Similar efficacy is seen with radiation therapy of pelvic metastases as compared to other sites; however, as compared to spinal radiation and radiosurgery, there is limited data regarding the RT treatment approach in the pelvis. Current guidelines recommend RT for painful osseous metastases as has been discussed and RT is useful in pelvic sites. In non-painful lesions involving the proximal femur and periacetabular region (zone 2), prophylactic radiation therapy may be considered to reduce the risk of local progression. This approach is often utilized in clinical practice, especially if the patient already requires treatment of another painful location; however it is not recommended based on current treatment guidelines. Further investigation of this approach is warranted to decrease the risk of local progression and the resultant morbidity. Lesions involving zones 1, 3, and 4 may not benefit from XRT prophylaxis unless they exist in close proximity to a sacral nerve root in zone 4.

Postoperative RT to the pelvis is generally offered 10–14 days after THR and is supported by guidelines. In some cases, a patient may not be referred for RT consideration given concerns with wound healing and the relative risk of postoperative complications. In a series of patients treated with combination therapy, the addition of RT was the most significant factor in patients achieving durable functional improvement and was associated with fewer second orthopedic procedures at the same site as well as improved survival (Townsend et al. 1995). While intrinsic

bias exists, the reduction in second surgical procedures indicates that the local control achieved with postoperative RT exceeds the risks of wound complications that may require additional surgical intervention.

7 Conclusion

The management of solid tumor bone metastases is complex and requires a team approach with input from multiple medical specialists. Ideally, complex cases can be discussed in the context of multidisciplinary tumor boards where cases can be reviewed in detail and discussed prior to intervention. While this is clearly not feasible for every case, many, especially those where instability exists, require a measured approach as is detailed in this chapter. Orthopedic oncology is primarily a palliative field and practitioners with experience understand the importance of quality of life and functional independence as it relates to treatment management. Despite this, many controversies persist and require further investigation to clarify the role for each subspecialist. As fields advance treatment recommendations change, as is most evident in the field of spinal metastases and spine radiosurgery. Recent evidence suggests that aggressive ablative local therapy may also improve overall survival in patients presenting in the oligometastatic state which may further evolve the field of orthopedic oncology to a more definitive mindset.

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Oligometastatic Disease

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Abstract

Metastatic cancer patients represent a highly heterogeneous cohort with widely differing prognoses. The application of local, metastasis-directed therapies is becoming increasingly appealing, but controversies regarding patients most likely to benefit from these interventions remain. This chapter aims to evaluate the phenomenon of the oligometastatic state, rationales for utilizing local therapy (surgical and radiotherapeutic), as well as summarize the available evidence thereof. A discussion on interactions of local therapy with immunotherapy, ongoing clinical trials, and optimal patient selection is also conducted.

1 Introduction

Systemic neoplastic metastasis is a major cause of death in cancer patients. However, it has long been known that not all patients with metastatic cancer experience early mortality; studies have documented subsets of patients who experience longer-term survival that would otherwise not be predicted by clinical stage alone (Falkson et al. 1990; Greenberg et al. 1996). Moreover, prognosis of metastatic cancers is improving in the modern era for several reasons, such as improved diagnostic capabilities to more accurately detect

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and monitor metastatic deposits, as well as improved systemic therapy options with which to more adequately control systemic disease (Giordano et al. 2004; Dawood et al. 2008).

Given that a proportion of metastatic cancer patients experience longer-term survival, which is related to the number of metastatic sites, the term "oligometastases" was first popularized in the mid-1990s. This term refers to an "intermediate" state of stage IV cancer in which systemic disease is limited to a few known sites (Hellman and Weichselbaum 1995). Although the number of sites encompassed by the "oligometastatic" definition varies based on the publication, a generally accepted definition is ≤5–6 sites (which is not equivalent to 5–6 organs). Oligometastases may also be subdivided based on timing; metastases presenting at the same time (or within a nominal time period of each other) are often referred to as synchronous oligometastases, whereas subsequent development of metastases is often termed as metachronous metastases.

Although palliative systemic therapy has historically been the mainstay of metastatic cancer, owing to the improved prognosis of patients with oligometastatic disease, performing definitive local therapy to the primary and areas of oligometastases is a major area of ongoing investigation. This chapter summarizes the available evidence on, as well as posits ongoing challenges in, the management of oligometastatic disease.

2 Rationale for Local Therapy

The foremost reason to perform aggressive, definitive local therapy to sites of limited metastatic disease is that subsets of patients achieve prolonged survival even if definitive therapies are not delivered. These patients likely have favorable prognostic factors such as young age, good performance status, limited number and/or volume of metastases, and favorable tumor biology (with or without a good response to systemic therapy). Hence, one rationale in these patients is the general oncologic principle that aggressive management is most indicated and/or optimal for patients who are more likely to survive long enough to experience the benefits of those aggressive therapies.

Next, it is well known for many tumor types that there is a "gray area" of survival between very advanced nonmetastatic disease and stage IV disease. For instance, the survival of stage IIIB non-small cell lung cancer (NSCLC) is numerically very comparable to stage IV cases (Pfister et al. 2004; De Cos Escuin et al. 2004; Fry et al. 1999; Wang et al. 2010). This beckons the question that if stage IIIB cases are treated definitively, should better-prognostic subsets of stage IV disease not achieve comparable—if not superior—survival to IIIB patients?

Additionally, patterns-of-failure studies following initial systemic therapy for stage IV NSCLC indicate that areas of subsequent progression are the same as those where initial metastatic deposits were located (Rusthoven et al. 2009a). This implies that if the known areas of metastatic disease are definitively treated, the rate of out-of-field progression (hence linked to the "futility" of local therapy in this setting) is relatively low. This is likely true to an even greater degree in contemporary time periods when the quality and variety of available systemic therapy compounds are at an unprecedented high.

3 Surgical Metastasectomy

Surgical approaches to oligometastatic disease have been studied for over three decades, most notably so for liver and lung metastases. Although all retrospective studies and most non-randomized studies carry selection and/or enrollment biases (thus limiting applicability to a "general" stage IV population), all similarly illustrate that well-selected patients undergoing local therapy can achieve numerically high long-term survival.

Four notable, high-volume studies of resection for hepatic metastases from colorectal cancer demonstrated 5-year overall survival (OS) ranged from 28 to 58% (Hughes et al. 1986; Nordlinger et al. 1996; Fong et al. 1999; Pawlik et al. 2005). It is important to recognize that the vast majority of patients from these studies did not undergo

optimal pretreatment diagnostic imaging (e.g., magnetic resonance imaging (MRI) and/or positron emission tomography (PET)), indicating a lower level of confidence (by today's standards) that there was truly no other known micrometastatic disease in the liver and/or elsewhere in the body at the time of diagnosis. This implies that survival figures for analogous populations may be higher in the modern era.

The first randomized study of local therapy for liver metastases from colorectal cancer was the European Organisation for the Research and Treatment of Cancer (EORTC) 40004 study (Ruers et al. 2017). This trial randomized 119 patients with fewer than ten liver metastases to systemic therapy (FOLFOX ± bevacizumab) with or without radiofrequency ablation and/or resection. At median follow-up of 10 years, 5-year OS in the systemic therapy group was 30% vs. 43% in the local+systemic therapy arm ($p = 0.01$). Of note, the rate of extrahepatic progression was statistically similar in both arms, affirming the results of the aforementioned studies (Rusthoven et al. 2009a).

Metastasectomy for lung lesions has also resulted in similar findings from two large retrospective studies. An investigation of 4572 patients from an international database of several diverse histologies displayed a 5- and 10-year OS of 36 and 26%, respectively, following complete resection of a metastatic lesion to the lung, confirming the efficacy and safety of metastasectomy (Pastorino et al. 1997). Of note, cases with a single metastatic lesion were independently associated with a better prognosis. Another study of a large, institutional database of 539 sarcoma patients with lung metastases displayed a 5-year OS of 34% (Chudgar et al. 2017).

4 Stereotactic Body Radiotherapy

Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), delivers high doses of radiation to a focused volume over a few fractions. This is associated with increased target conformality, patient convenience, and tolerability profiles. Because metastasectomy may be associated with surgical-related morbidities, post-therapy hospitalization, and/or a decrease in functional organ reserve capacity, SBRT is an attractive therapeutic option in the oligometastatic setting.

The efficacy of SBRT for oligometastatic liver and lung lesions is roughly comparable to metastasectomy, as shown by two multicenter phase I/II trials both illustrating the 2-year (actuarial) local control (LC) to be over 90% with a <5% rate of grade 3+ toxicities (Rusthoven et al. 2009a; Rusthoven et al. 2009b). Although the aforementioned studies were not "true" oligometastatic trials in that the other areas of metastases were not necessarily required to be treated in a protocol-specific fashion, they provided early evidence of the safety and efficacy of SBRT for 1–3 lung or liver metastases. A retrospective review from Germany on 700 patients treated with SBRT for medically inoperable lung metastases demonstrated a 2-year local control of 81.2% and 2-year OS of 54.4%, leading the authors to conclude that SBRT was an option for definitive local control in patients with metastatic disease to the lungs (Rieber et al. 2016). A review of the SBRT database of the German Society of Radiation Oncology (DEGRO) demonstrated 1- and 2-year local control rates for patients with liver oligometastases treated with SBRT of 77% and 64%, with greater local control rates associated with maximum isocenter biologically effective dose >150 Gy (Andratschke et al. 2018). SBRT has been demonstrated to improve local control for patients with bony metastatic disease in both the spine and the appendicular skeleton, with local control rates approaching 90% (Husain et al. 2017; Owen et al. 2014). SBRT has been used in the setting of oligometastatic renal cell cancer (RCC). The ablative doses delivered using SBRT are able to overcome the radioresistance of RCC, with one review having reported 2 year local control of RCC metastases treated with SBRT of 91.4% with no treatment limiting toxicities (Ranck et al. 2013). The use of SBRT to distant metastatic sites has also been described in the setting of oligometastatic prostate cancer, with Azzam et al. reporting a median OS of

>3 years after SBRT delivered to patients with ≤4 lesions (Azzam et al. 2015).

SBRT (and radiotherapy in general) is additionally important to enhance systemic antitumoral immune responses, a rapidly emerging concept that has major implications for delivery of immunotherapeutic compounds. Tumor cells express several proteins that promote a relative degree of immune quiescence, thereby potentiating cellular growth by decreasing the likelihood of immune-mediated neoplastic destruction. Many immunotherapeutic compounds inhibit some form of this tumor cell—immune cell blockade. However, an underappreciated phenomenon with respect to immuno-oncology is that radiotherapy-mediated antigen presentation likely enhances the antitumoral immune response as well as the efficacy of immunotherapy (Formenti and Demaria 2009). Moreover, emerging preclinical data suggest that ablatively dosed RT promotes greater antineoplastic immune effects (Vanpouille-Box et al. 2017). Therefore, the implication that these data provide is that combined SBRT-immunotherapy may result in improved outcomes (e.g., higher progression-free survival (PFS) and/or lower rates of new metastatic deposits) than immunotherapy alone (Shaverdian et al. 2017).

5 Prospective Evidence

A single-arm phase II trial from Holland enrolled 40 NSCLC patients with <5 metastatic sites at the time of diagnosis; all patients underwent PET and MRI imaging, and most (87%) patients had 1 metastasis (most frequently intracerebral) (De Ruysscher et al. 2012). Locoregional and distant disease were required to be addressed with radiotherapy (conventionally fractionated, or stereotactic radiosurgery for cerebral disease) or surgery. The trial met its prespecified primary endpoint of 2-year OS being greater than 20% (23% in the study). Although 80% of patients that recurred did so out-of-field(s), this may be contextualized by patient selection as well as results of subsequent studies. Additionally, the majority of patients did not receive up-front chemotherapy followed by local therapy, indicating that further refinement based on treatment response and tumor biology was largely not possible.

An investigation from the University of Rochester assessed 121 subjects with ≤5 sites of metastasis, although most (76%) of patients had a single organ of involvement (Milano et al. 2012). Of note, unlike the prior trial, all patients were treated with SBRT (most commonly 50 Gy in 5 fractions). In part because this cohort encompassed patients with a wide variety of histologies (including nearly one-third of patients with breast cancer), 2-year OS (50%) was substantially higher than in the prior NSCLC study. At median 4.5 years follow-up, however, the 4-year freedom from out-of-field metastases was similar to the previous study (26%). Although breast cancer histology played a major role in LC and OS, there was a strong trend ($p = 0.055$) noted with regard to improved OS in patients with one (as compared to >1) metastasis.

A single-arm phase II trial from Belgium will be next described (Collen et al. 2014). The purpose of the study was to determine the long-term outcomes for patients with oligometastatic NSCLC who underwent SBRT to each metastatic lesion. Of 26 cases, 17 received induction chemotherapy (two had driver mutations and were treated with targeted agents) and 9 did not (largely owing to intolerance and/or medical unsuitability). Two of the 17 patients progressed on chemotherapy but were included in the analysis. Although inclusion criteria were 5 or fewer metastatic lesions, a majority of patients had 1 site of metastasis. The prescription SBRT dose was 50 Gy in 5 fractions, and median follow-up was 16 months. The median progression-free survival (PFS) was 11.2 months, and median OS was 23 months, which was correlated on univariate analysis with receipt of induction therapy. The authors of the study concluded SBRT to oligometastatic sites was a reasonable option given the durable local control and meaningful long-term OS.

A phase II study from the University of Texas Southwestern (UTSW) and the University of Colorado also sought to determine if SBRT delivered to all sites of disease along with the concurrent use of erlotinib in patients with

oligometastatic NSCLC would delay relapse of disease (Iyengar et al. 2014). The inclusion criteria was a diagnosis of NSCLC with ≤6 non-cerebral metastases that progressed on first-, second-, or third-line chemotherapy. Patients received SBRT (19–24 Gy in 1 fraction, 27–33 Gy in 3 fractions, 35–40 Gy in 5 fractions) to all sites of disease with concurrent and adjuvant erlotinib. However, epidermal growth factor receptor (EGFR) status was not required to be positive for protocol enrollment. At median follow-up of 12 months, median OS was 20 months. Three of 21 analyzable patients failed in-field, as compared to ten out-of-field areas. A notable predictor of PFS included treatment of the primary disease; a predictor of OS was number of metastatic sites.

Much of the prospective evidence describing the safety and efficacy of definitive treatment for oligometastatic disease lies in single-arm, non-randomized trials. However, two important randomized trials that compared outcomes between definitive local treatment to oligometastatic sites versus observation provide strong evidence for the benefit of aggressive local treatment in the setting of oligometastatic disease. The first of these randomized trials was a Phase II randomized trial conducted at MD Anderson, the University of Colorado, and the London Health Sciences Center. This trial enrolled 49 oligometastatic NSCLC patients, with the primary endpoint of PFS (Gomez et al. 2016). Oligometastases in that study referred to ≤3 sites of metastases following induction systemic therapy (not including the primary). Of note, intrathoracic lymph nodes were counted as one site (if present), and brain metastases that required immediate treatment prior to induction therapy also contributed to the total (each metastasis being counted separately). All patients received induction systemic therapy (platinum doublet chemotherapy, erlotinib if EGFR mutation was present, or crizotinib if Anaplastic Lymphoma Kinase (ALK) rearrangement was present). Provided there was no progression, patients underwent imaging (non-mandated use of brain MRI or PET) and were subsequently randomized to either local therapy to all sites of metastasis (SBRT, hypofractionated radiotherapy, conventionally fractionated radiation, or surgery) or maintenance therapy with either continued systemic chemotherapy or observation. Subjects that underwent local therapy experienced improved PFS (p = 0.005) and freedom from new (out-of-field) lesions (p = 0.049). Median OS had not been reached in either group at the median follow-up of 12 months, although a recent update of that trial (in abstract form at the time of writing of this chapter) did demonstrate an OS benefit (Gomez et al. 2018). Hence, the results of this study were particularly noteworthy in that PFS was increased with local therapy, thus implying a "proof-of-principle" that existing areas of disease are more likely to progress. Moreover, an important finding was that local therapy statistically decreased the rate of out-of-field recurrences; whether this could be attributed to the abscopal effect is uncertain, however.

The second randomized trial was recently reported by investigators from UTSW (Iyengar et al. 2018). In this trial, patients with oligometastatic NSCLC, defined as ≤6 non-cerebral metastases (three lesions at most in the liver and lung each) were randomized to either SBRT to all sites of disease or observation following induction chemotherapy. Patients initially underwent 4–6 cycles of induction chemotherapy (targeted therapies were not given in that setting); provided no progression, patients (n = 29) were randomized between maintenance chemotherapy (oncologist's discretion) and maintenance chemotherapy plus SBRT. Although 45 Gy in 15 fractions was appropriate if normal tissue constraints could not be met, SBRT doses/fractionation included 21–27 Gy in 1 fraction, 27–33 Gy in 3 fractions, 30–38 Gy in 5 fractions). The SBRT arm was associated with higher PFS (10 months vs. 4 months, p = 0.01), and the trial was stopped early after interim analysis found a significant PFS improvement with local treatment. Median OS between groups was not statistically evaluable at median follow-up of 10 months (not reached vs. 17 months). Of note, there were no statistical differences in survival between patients with ≤2 vs. >2 metastatic lesions, or presence vs. absence of previously treated brain metastases.

At the time of writing of this chapter, the randomized phase II SABR-COMET trial was published in abstract form only and enrolled 99 patients with oligometastatic (1–6 lesions) disease from controlled primaries (Palma et al. 2018). Ninety-two percent of patients had 1–3 metastatic lesions. The most common histologies were breast, lung, colorectal, and prostate cancers. As compared to palliative standard-of-care treatments (per clinicians), SBRT to oligometastases improved OS (the primary endpoint), with respective median values of 28 and 41 months, respectively.

As mentioned previously, the use of SBRT may cause increased tumor antigen release, which can subsequently improve T-cell infiltration of the tumor by improved tumor antigen presentation and recognition by the immune system. Investigators from the Netherlands sought to determine if the addition of SBRT on a single metastatic lesion in patients with NSCLC could lead to an increased tumor response (Theelen et al. 2018). Patients with advanced NSCLC who had progressed on at least two lines of chemotherapy were randomized to SBRT to a single metastatic site to a dose of 24 Gy in 3 fractions in addition to pembrolizumab versus pembrolizumab alone. Median PFS was 6.4 months in the SBRT arm vs. 1.8 months in the control arm ($p = 0.04$). At 12 weeks, the overall response rate (ORR) was 41% in the SBRT arm vs. 19% in the control arm, leading the authors to conclude that SBRT was a well-tolerated and effective method to improve antitumor response when used along with checkpoint blockade.

The histology of disease is an important consideration in determining whether or not to offer local treatment in the setting of oligometastatic disease. NRG Oncology Radiation Therapy Oncology Group 0937 was a trial that compared prophylactic cranial irradiation (PCI) alone to PCI and consolidative extracranial irradiation (cRT) in patients with ≤4 extracranial metastases for patients with extensive stage small cell lung cancer (Gore et al. 2017). No difference was observed between the PCI alone and PCI + cRT arms in 1 year OS or rates of progression at 3 months and 12 months, though patients receiving cRT did have delayed time to progression.

6 Patient Selection

The population of stage IV cancers is very heterogeneous, and therefore selecting patients most likely to experience long-term survival is paramount to evaluate whether a benefit from aggressive local therapy is derived. Based on the aforementioned retrospective and prospective data, there are several important variables that clinicians must consider when assessing an oligometastatic patient for local therapy. Although there are numerous variables that contribute to the "entire clinical picture" of a patient, we posit that five factors may be more important in terms of relative "priority."

First, number of metastases is substantial to assess, noting that multiple (but not all (Iyengar et al. 2018)) aforementioned studies illustrated that patients with one metastasis experience longer survival. Hence, these patients should ideally be treated most aggressively, if possible. Although most data exists for up to three metastases, it should be noted that >1 site, and certainly >3 sites, may reduce the incremental benefit. However, this statement carries caveats such as how to categorize one metastasis (e.g., some studies count any mediastinal nodes as one site, versus others have counted each station as one site) as well as chronicity (most data exist for synchronous metastases, but metachronous disease may allow for more aggressive therapy). Additionally, the aforementioned study by Iyengar et al. included patients with up to five metastatic sites. Nevertheless, patients with 1–3 sites should be further evaluated for several other parameters as described below.

Second, response to induction systemic therapy is arguably just as important, as biological factors related to induction therapy resistance are also highly likely to portend a poor prognosis; moreover, both known randomized trials excluded patients with progression on first-line induction therapy for this very reason. Using NSCLC as an example, first-line treatments include chemotherapy, targeted agents, or checkpoint inhibitors; hence, progressors on these therapies would be unlikely to benefit from local therapy.

Third, patient-specific factors should also be assessed, namely age and performance status. Both are well known to be independent prognostic factors for survival, so patients with advanced age and/or poor performance status may benefit from local therapy to a lesser degree. The median age of patients in most of the aforementioned studies was less than 70, but it is acknowledged that patients can be "functionally younger" or "functionally elderly." This being said, most patients in the previously described investigations had a Zubrod performance status of 0–1, as it is less likely that patients with scores of 2–3 would benefit from local interventions.

Fourth, histopathologic factors play a role to some degree. Although there have been fewer mentions of poor-prognostic histopathologic factors, NSCLC patients with EGFR mutations (or potentially ALK/ROS rearrangements) are associated with improved prognosis and should be treated more aggressively. Moreover, with NSCLC histologies as the reference, patients with certain histologies that are known to have better prognosis (e.g., breast, prostate, possibly p16+ head/neck cancers) may also benefit to a greater degree with definitive treatment to oligometastatic sites. Importantly, patients with histologies that have a more diffuse metastatic pattern, such as small cell lung cancer, may benefit less with definitive treatment.

Lastly, for patients with NSCLC, the presence of mediastinal nodes also correlates with poorer survival from some of the aforementioned data as well as a meta-analysis (Ashworth et al. 2014). Although intrathoracic T classification has been cited as well as a poor prognostic factor (albeit with fewer data), the presence of N2+ nodes implies a higher rate of occult metastatic seeding, and is another important factor in evaluation.

Taken together, although these five factors are general assessments, it is difficult to assign priority and/or quantitate their relative importance. As such, patients that meet an intermediate (e.g., 2–3) of the above criteria remain a major "gray zone" for local metastasis-directed therapy, indicating that although this heterogeneous group of patients can be attempted to be lumped into discrete groups, the oligometastatic setting will likely remain an "art" rather than a "science" for the foreseeable future.

7 Ongoing Clinical Trials

A few of the currently ongoing and accruing randomized trials are included in Table 1. This table was not intended to provide a comprehensive list

Table 1 Example ongoing trials examining radiotherapy for oligometastatic disease

Trial name/number	Phase	Accrual goal	Histologies allowed	Number of oligometastases allowed	Trial arms	Primary endpoint
NRG-LU002/ NCT03137771	II/III	300	NSCLC	≤3 metastases	Chemotherapy versus SBRT to all sites followed by chemotherapy	Progression-free survival Overall survival
NRG-BR002/ NCT02364557	II/III	402	Breast	≤2 metastases	SOC *versus* SBRT and/or surgery of metastatic sites	Progression-free survival Overall survival
CORE/ NCT02759783	II/III	206	Breast, prostate, NSCLC	≤3 metastases	Standard of care versus SBRT to all sites followed by the standard of care	Progression-free survival
STEREO-STEIN/ NCT02089100	III	280	Breast	≤5 metastases	Physician's discretion versus SBRT to all sites	Progression-free survival
SARON/ NCT02417662	III	340	NSCLC	≤3 metastases	Chemotherapy versus chemotherapy + radiotherapy (conventional or SBRT) to the primary and SBRT to the metastatic sites	Overall survival

of all the ongoing trials. Instead, the purpose was to highlight important trials that will likely significantly impact our understanding of how oligometastatic should be treated.

A discussion of the specified trials brings up a few important details. First, although up to 5–6 metastases have been included in the definition of oligometastatic disease, the majority of trials include patients with three or fewer metastatic sites. Undoubtedly, part of the reason for this is an attempt to select the patients that would most likely benefit from treatment of all their metastases and obtain a statistically significant result. If these trials demonstrate effectiveness, future trials will likely expand on these results and try to examine the benefit of treatment of a greater number of metastases (i.e., >5 metastatic sites). Second, the highlighted trials have large accrual targets (dwarfing the numbers reported in the currently published literature) and were designed to include the most common types of cancers (NSCLC, breast, and prostate cancers). By deciding to include the most prevalent histologies, these trials have a good chance of meeting their accrual numbers. This is an overlooked point; without steady and complete accrual, these trials would not be able to provide a concrete answer on the role of local treatment for oligometastatic disease and leave the current debate unsettled.

While the clinical outcomes of these trials are certainly very important to understand the role of radiotherapy in oligometastatic disease, determining the outcomes on a biologic, immunologic, and molecular level will be an essential component of ongoing and future research. One such trial looking to collect data on this topic is the ORIOLE trial (Radwan et al. 2017). In this randomized, non-blinded phase II trial, 54 men with oligometastatic (≤3 metastases) prostate cancer will be randomized to observation or SBRT. Patients in the observation arm will undergo baseline testing including collection of circulating tumor DNA (ctDNA) at 0, 90, and 180 days. The SBRT arm will also have ctDNA levels collected before (day 0) and after SBRT (day 90 and day 180) as well as counts of circulating tumor cells (CTCs). In addition, quantitative sequencing of T-cell receptor (TCR) repertoires will be performed for the SBRT arm at day 0 and day 90. This testing will be very valuable in determining the effect of SBRT on the presence of circulating, micrometastatic disease and the immune system. Incorporation of this type of molecular and immunologic testing into current and soon to-be-open trials should be a strong consideration.

8 Conclusion

Metastatic cancer patients represent a highly heterogeneous cohort with widely differing prognoses. There exists a cohort of patients with limited metastatic disease (oligometastatic disease) who may benefit from addition of local therapies such as surgery and radiotherapy. The current, albeit limited, evidence suggests there may be a role for radiotherapy in the form of SBRT to sites of oligometastatic disease. Large, currently ongoing clinical trials will likely provide a more definitive answer on the role of SBRT and will shape the future of care for these patients.

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Rectal Cancer

Ann Raldow and Jennifer Wo

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Abstract

Radiation therapy has a well-established role in the treatment of locally advanced, clinically node-positive rectal cancer. Radiation therapy has been demonstrated in numerous randomized trials to decrease the rates of local failure. There are two radiation treatment schemas which have been proven to be effective, including standard fractionated chemoradiation and short-course radiation therapy. More recent studies are evaluating the potential impact of omission of radiation therapy and surgical resection, respectively, for favorable-risk locally advanced tumors.

1 Introduction

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in both men and women in the United States (Siegel et al. 2014). In 2014, there were 136,830 new cases of colorectal cancer in the United States; of these, 28% was cancer of the rectum (Siegel et al. 2014). Surgery is at the cornerstone of curative therapy for patients with resectable rectal cancer. Most patients present with tumors that are mobile and invasive into or beyond the rectal wall, requiring surgical resection with either a low anterior resection (LAR) or abdominoperineal resection (APR), depending on the size, location, and extent of the cancer. A small percentage of

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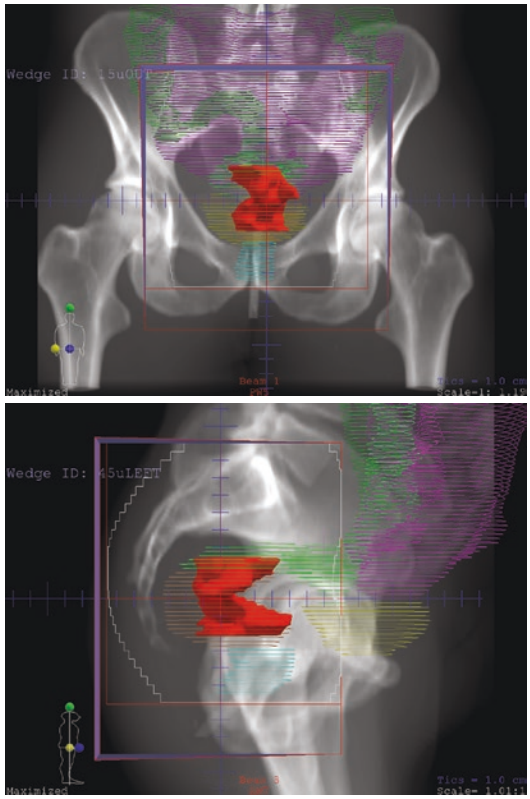

Fig. 1 Standard radiation fields for rectal cancer (courtesy of Theodore Hong)

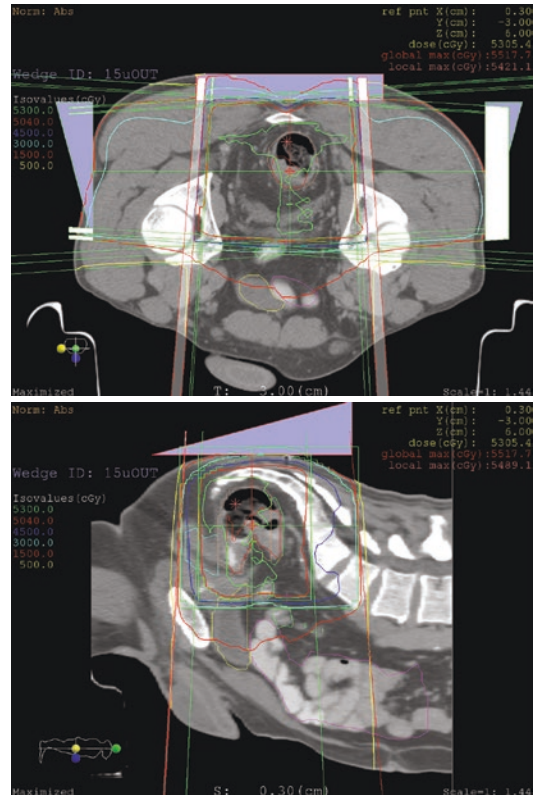

Fig. 2 Standard three-field radiation plan for rectal cancer (courtesy of Theodore Hong)

patients present with locally advanced, unresectable tumors that are adherent or fixed to adjoining structures such as the sacrum, pelvic sidewalls, prostate, or bladder.

Although patients with resected stage I disease have excellent prognoses with surgery alone, locoregional failure after surgery alone in patients with transmural or node-positive tumors is unacceptably high. Several randomized trials were designed to improve the results of surgery alone through the addition of radiation therapy, and these reported significant reductions in local recurrence (Folkesson et al. 2005; Peeters et al. 2007; Gastrointestinal Tumor Study Group 1985). Early trials of multimodality therapy in rectal cancer evaluated postoperative radiation with or without chemotherapy, but the role and sequencing of these therapies have changed over time (Fisher et al. 1988). More recently, neoadjuvant treatment is more common as it results in better local control, increased likelihood of sphincter preservation, and a lower risk of chronic anastomotic stricture. Figures 1 and 2 represent standard radiation treatment fields for rectal cancer.

There are two strategies to preoperative therapy for patients with T3-4 or node-positive rectal cancer: short-course radiation and long-course chemoradiation (CMT). While the radiation techniques are comparable, the radiation schedule and timing of resection differ. Typically, short-course radiation consists of 25 Gy in five fractions followed by surgery 1 week later. Long-course CMT consists of 50.4 Gy in 28 fractions with concurrent fluoropyrimidine chemotherapy, followed by surgery in 4–8 weeks. Although short-course radiation therapy is used in northern European countries and Scandinavia where it was developed, it is not favored in North America and several other European countries because it cannot be com-

bined with concurrent chemotherapy. Proponents of each of these approaches base their treatment decisions on the results of several recently published randomized trials.

2 Short-Course Radiotherapy

Two key trials support the use of short-course preoperative radiation versus surgery alone for resectable rectal cancer. The Swedish Rectal Cancer Trial randomized 908 patients with stage I–III disease to short-course radiation followed by surgery or surgery alone (Folkesson et al. 2005; Birgisson et al. 2005; Swedish Rectal Cancer Trial et al. 1997). With a median follow-up of 13 years, preoperative radiation significantly decreased the rate of local recurrence (9% vs. 26%, $p < 0.001$) and increased the rates of overall survival (38% vs. 30%, $p = 0.008$). Of note, this was the first and only trial that revealed a significant improvement in survival with short-course preoperative radiation. However, the study did not require total mesorectal excisions (TME) and disease stage was not balanced between the two arms.

The high local recurrence rate in the preoperative arm of the Swedish Rectal Cancer Trial motivated the Dutch to perform the CKVO 95-04 trial, which used the same design to randomize 1861 patients, but required total mesorectal excisions (Peeters et al. 2007; Kapiteijn et al. 2001; Van Gijn et al. 2011). With a median follow-up of 5 years, preoperative radiation significantly decreased the rate of local recurrence (5.6% vs. 10.9% at 5 years); however, there was no significant difference in cancer-specific or overall survival.

3 Long-Course/Standard Fractionation Radiotherapy

Advocates of long-course CMT quote the results of two important randomized trials: the German Rectal Trial and NSABP R-03. In fact, only 3 years after the CKVO 95-04 trial was published, the results of the German Rectal Cancer trial were reported. The German Rectal Trial randomized 823 patients to either preoperative long-course CMT with concurrent CI 5-FU or the same treatment in the postoperative setting with an added 5.4 Gy boost (Sauer et al. 2004, 2012). The patients were required to undergo TME and four cycles of adjuvant 5-FU chemotherapy were planned. Both the initial and long-term follow-up publications showed significant decreases in local failure (5-year local failure rate of 6% vs. 13%), acute and long-term toxicity, and sphincter preservation with preoperative CMT. However, there was no difference in overall survival. Of note, a large minority (18%) of patients in the postoperative treatment arm were found to have stage I disease at surgery. This trial established preoperative long-course CMT as the standard of care for patients with cT3–4 and/or node-positive rectal cancer.

In the United States, the results of the German Rectal Trial were confirmed with the NSABP R-03 study, where 256 patients were assigned to either preoperative long-course CMT with concurrent 5-FU or the same treatment in the postoperative setting (Fisher et al. 1988). Patients received an additional three cycles of adjuvant 5-FU chemotherapy, but TME was not required. Although the study was closed early due to poor accrual, patients in the preoperative CMT arm had a significantly improved 5-year DFS (74.5% vs. 65.6%) and a nonsignificant trend towards improved 5-year OS (74.5% vs. 65.6%, $p = 0.065$). There was no difference in locoregional recurrence (11% in both arms). Patients in the preoperative CMT arm had a significant reduction of pathologic lymph node involvement and a pCR of 15%. Together, the German Rectal Trial and the NSABP R-03 study show improved LC and superior rates of sphincter preservation in patients undergoing preoperative long-course CMT as compared to postoperative therapy.

4 Randomized Trials of Short-Course Versus Long-Course CMT

The first randomized trial comparing preoperative short-course radiation therapy with long-course CMT with 5-FU/LV in patients with

resectable cT3 disease was the Polish Rectal Study (Bujko et al. 2004, 2006). Although the long-course CMT arm had a lower incidence of positive radial margins (4% vs. 13%, $p = 0.017$), there was no difference with respect to local recurrence, sphincter preservation, or survival. However, the study has several limitations that deserve consideration. In the study, TME was performed for distal tumors only, postoperative chemotherapy was optional, there was no consistency in pre-therapy staging evaluation, and there was no radiation quality-control review. In addition, there was surgeon subjectivity with respect to whether patients underwent sphincter preservation (5/18 patients underwent an APR after a clinical complete response following preoperative CMT) and the study was underpowered to detect differences in local control and survival.

Ngan et al. published a similar trial from Australia (TROG 01-04), where 326 patients with T3 rectal cancer (56% were N0) were randomized to short-course radiation versus long-course CMT with 5-FU, followed by surgery (Ngan et al. 2012). In contrast to the Polish Rectal Study, patients were scheduled to receive 6 months of postoperative chemotherapy. There were no significant differences in 3-year local recurrence (7.5% vs. 4.4%), 5-year distant recurrence (27% vs. 30%), or 5-year overall survival (74% vs. 70%) between the short-course and long-course arms, respectively. Likewise, there were no significant differences in late radiation toxicity. However, the study included a relatively small number of patients and was not powered to show equivalence. In addition, there was short follow-up and late local recurrences and toxicities can occur. Another key result that has not been presented is sphincter function.

5 Controversies Regarding the Preoperative Treatment

There is controversy as to the ideal preoperative treatment approach for patients with T3-4 or node-positive rectal cancer: short-course radiation and long-course CMT. These competing strategies have been proven effective in randomized trials and evolved in parallel. While short-course radiation was established in northern Europe and Scandinavia, long-course CMT evolved in the United States and several other European countries. Unfortunately, intertrial comparisons of the two different approaches were not feasible because the eligibility criteria varied; recent trials comparing the two approaches have significant limitations.

Proponents of short-course radiation point to patient convenience, lower cost, as well as lack of pathologic downstaging. Because the pathologic findings at the time of surgery are more likely to represent pretreatment staging, more appropriate adjuvant chemotherapy recommendations can be made. Sparing selected patients from adjuvant FOLFOX could potentially reduce treatment-related toxicity (e.g., long-term peripheral neuropathy) without compromising oncologic outcomes. Nonetheless, short-course radiation is not regularly recommended in the United States for patients with locally advanced rectal cancer because it cannot be safely combined with adequate doses of chemotherapy and does not increase sphincter preservation. In addition, there was some concern over long-term toxicity associated with the short-course regimen. Long-term toxicity data from these trials and quality-of-life comparison studies will be crucial in determining toxicity profiles for the two treatment strategies.

However, some of these limitations may be diminished by lengthening the time period between the completion of short-course radiation and surgery and giving chemotherapy either neoadjuvantly or after preoperative radiation. The Stockholm III trial is evaluating the consequences of increasing the interval between radiation and surgery (Pettersson et al. 2010). In this phase III trial, 303 patients were randomized to one of the three arms: short-course radiation and surgery within 1 week, short-course radiation and surgery after 4–8 weeks, and long-course radiation (50 Gy in 25 fractions) and surgery after 4–8 weeks. This trial will establish whether increasing the time interval between short-course radiation and surgery improves sphincter preservation and reduces toxicity.

In addition, there has been recent interest in defining the potential role of neoadjuvant chemotherapy without the use of routine radiation therapy for locally advanced rectal cancer. Schrag et al. recently evaluated the use of preoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX)-bevacizumab with selective use of radiation therapy prior to surgery in clinically staged II/III patients (Schrag et al. 2014). After chemotherapy, patients with stable or progressive disease were to have preoperative radiation, whereas responders were to proceed immediately to TME. In addition, postoperative radiation was planned if there was not a R0 resection. Administration of six cycles of adjuvant FOLFOX was recommended. Of the 30 patients who completed preoperative chemotherapy, all had tumor regression and proceeded to immediate TME without preoperative radiation therapy. The pathologic complete response rate with chemotherapy alone was 25% (95% CI, 11–43%) and the 4-year local recurrence rate was 0% (95% CI, 0–11%). These results suggest that neoadjuvant chemotherapy with selective radiation does not compromise outcomes. A phase III trial (PROSPECT) to validate this study is currently under way.

The ideal treatment management for patients with locally advanced rectal cancer is debatable. While short-course radiation and long-course CMT are established treatment paradigms, the role and sequencing of radiation, chemotherapy, and surgery continue to change with time. The results from trials evaluating additional treatment approaches will be revealing. To ultimately assume the optimal treatment approach, it is crucial that we better do preoperative radiographic assessment of postoperative high-risk pathologic features. In addition, we need to improve our evaluation of the molecular profile of rectal cancers, which holds the potential of proper identification of patients at high risk of recurrence and, therefore, suitable for the receipt of adjuvant treatment. In the meantime, at our institution, we treat locally advanced rectal cancer patients with long-course CMT using concurrent 5-FU followed by TME 4–6 weeks later, as well as 4–6 months of adjuvant 5-FU-based chemotherapy.

6 Future Directions: Minimizing Therapy with the Wait-and-See Approach

Although the standard of care for patients with locally advanced rectal cancer is chemoradiation followed by TME and adjuvant chemotherapy, there has recently been increasing interest in treatment de-escalation. Preoperative chemoradiation produces pathologic complete response in approximately 10–20% of patients; therefore, a subgroup of rectal cancer patients may not need surgery after chemoradiation. Although it is challenging to determine which patients will have a pathologic complete response after chemoradiation, there are several analyses that have studied the feasibility of a watch-and-wait approach in patients with a clinical complete response to chemoradiation (Maas et al. 2011; Habr-Gama et al. 2004, 2006; Hughes et al. 2010; Smith et al. 2012).

Mass et al. performed one such study, in which they prospectively evaluated 21 patients with localized rectal cancer treated with chemoradiation (Maas et al. 2011). Patients were eligible for the study after confirmation of clinical complete response with magnetic resonance imaging (MRI), endoscopy, and biopsies. They were subsequently followed every 3–6 months with MRI, endoscopy, and computed tomography scans, so that local recurrences could be detected early. After a mean follow-up of 25 months, one patient developed a local recurrence and underwent salvage surgery. The remaining 20 patients survived without evidence of disease.

Although Mass et al. provide evidence in support of a watch-and-wait approach to the treatment of rectal cancer, there are challenges to this approach. For instance, present-day approaches to measuring tumor response are limited, and a clinical complete response does not necessarily denote a pathologic complete response. Careful patient selection, rigorous methods of evaluating clinical response, and close follow-up will be crucial to the success of this strategy. In the future, we hope that the wait-and-see approach will be evaluated in a randomized clinical trial.

Conclusion

For locally advanced, node-positive rectal cancer, neoadjuvant radiation therapy, either prescribed as neoadjuvant chemoradiation or short-course RT, is an effective treatment to achieve tumor downstaging and local control. Given concern for distant disease spread, more recent studies have looked at front-loading neoadjuvant chemotherapy and have even suggested a potential role for omission of RT in good responders. Additionally, for patients with a clinically complete response after definitive chemoradiation, an increasing number of studies are looking to evaluate the feasibility of a wait-and-wait nonoperative approach. For all of these approaches, careful patient selection and rigorous and close monitoring are necessary.

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Pancreatic Cancer

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Abstract

Pancreatic cancer is an aggressive disease with high rates of disease-related mortality due to high rates of systemic disease spread. The role of radiation therapy for pancreatic cancer has been controversial to date. There have been significant advancements in effective systemic therapy regimens and radiation treatment delivery techniques, however, that are promising. This chapter aims to review all pertinent literature regarding the role of radiation therapy for pancreatic cancer.

1 Introduction

In 2014, pancreatic cancer is estimated to represent 3% of new cancer cases (36,888 diagnosed cases) and to cause 7% of all cancer-related deaths (39,590 deaths) (Siegel et al. 2014). In contrast to the stable or declining trends for most cancer types, pancreatic cancer incidence rates are rising (Siegel et al. 2014). Prognosis is poor, with 5-year survival rates of only 6% (Siegel et al. 2014). Surgical resection is the only potentially curative treatment, and patients are categorized as resectable, borderline resectable, locally advanced, or metastatic. Approximately one-third of patients present with unresectable disease; for these patients, median survival is only 8–12 months.

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Locally advanced pancreatic cancer (LAPC) is characterized by encasement (>180° involvement) of the celiac and/or superior mesenteric artery and/or obstruction of the portal and/or superior mesenteric vein. The ideal treatment paradigm for these patients remains unclear. The National Comprehensive Cancer Network guidelines recommend single- or multiagent chemotherapy alone, or chemoradiation (preferably preceded by chemotherapy) (Tempero et al. 2014). The role of chemoradiation for LAPC has been one of the most hotly debated topics in oncology. The uncertainty lies in whether localized therapy is warranted given the tendency of LAPC to spread systemically.

2 Chemoradiation Versus Radiation Alone

Two trials compare the use of chemoradiation versus radiation therapy alone. Prior to the use of gemcitabine for patients with LAPC, the Gastrointestinal Tumor Study Group (GITSG) randomized 106 patients with LAPC to external beam radiation therapy (EBRT) (60 Gy) alone or concurrent EBRT (either 40 or 60 Gy) and bolus 5-FU (Moertel et al. 1981). The GITSG-9273 trial was stopped early when the chemoradiation arms were found to be superior. The 1-year overall survival rates were 11% for patients who underwent radiation alone compared to 38% for patients receiving chemoradiation with 40 Gy and 36% for patients receiving chemoradiation with 60 Gy ($p < 0.01$). After 88 additional patients were enrolled in the chemoradiation arms, there was a trend toward improved survival in the 60 Gy arm as compared to the 40 Gy arm ($p = 0.19$).

While the GITSG-9273 trial showed a survival benefit for chemoradiation, the Eastern Cooperative Oncology Group (ECOG) E8282 trial did not (Cohen et al. 2005). In this trial, 114 patients were randomly assigned to receive radiation therapy (59.4 Gy) alone or with concurrent infusional 5-FU (1000 mg/m^2 daily on days 2–5 and 28–31) plus mitomycin (10 mg/m^2 on day 2). The median survival was 7.1 months in the radiation-alone arm as compared to 8.4 months in the chemoradiation arm ($p = 0.16$). The authors concluded that the addition of 5-FU and mitomycin increased toxicity without improving OS. However, the absence of a survival benefit with chemoradiation in the ECOG study has been ascribed to variation in study design, including the surgical staging requirement and different chemotherapy regimens. A subsequent meta-analysis that included both of these studies demonstrated a survival benefit for chemoradiation (Huguet et al. 2009).

3 Chemoradiation Versus Chemotherapy Alone

As it became evident that radiation therapy alone was insufficient, investigators evaluated the role of chemoradiation versus chemotherapy alone. The Fédération Francophone de Cancérologie Digestive-Société Française de Radiothérapie Oncologie (FFCD-SFRO) trial randomized 119 patients to chemoradiation (60 Gy in 2 Gy fractions with 300 mg/m^2/day of continuous-infusion 5-FU on days 1–5 for 6 weeks and 20 mg/m^2/day of cisplatin on days 1–5 during weeks 1 and 5) or gemcitabine (1000 mg/m^2 weekly for 7 weeks) (Chauffert et al. 2008). Patients in both arms received maintenance gemcitabine until disease progression or toxicity necessitated discontinuation. Although the study initially targeted accrual of 176 patients, the study was closed early after interim analysis demonstrated worse survival among patients randomized to receive chemoradiation. Median survival was superior in the gemcitabine arm (13 vs. 8.6 months, $p = 0.03$). In a per-protocol analysis of patients who received at least 75% of the planned treatment, the median survival was still only 9.5 months for the chemoradiation patients. In addition, there were more grade 3–4 toxicities recorded in the chemoradiation arm (36% vs. 22%). The authors concluded that chemoradiation with 5-FU is more toxic and less effective than gemcitabine alone. Of note, the dose intensity of maintenance gemcitabine was significantly lower in the chemoradiation arm because of more hematological toxicities.

The results of the ECOG E4201 study stand in contrast to the results of a study from the (FFCD-SFRO) trial. In the ECOG E4201 trial, 74 of a planned 316 patients were randomly assigned to either gemcitabine alone (1000 mg/m^2 × 7 cycles) or gemcitabine (600 mg/m^2) with 50.4 Gy of radiation followed by gemcitabine (1000 mg/m^2 × 5 cycles) (Loehrer et al. 2011). Median survival was superior in the chemoradiation as compared to the gemcitabine-alone arm (11.1 vs. 9.2 months, one-sided $p = 0.017$). As expected, grade 4–5 toxicities were more frequent in the chemoradiation arm as compared to the gemcitabine-alone arm (41% vs. 9%). The authors concluded that chemoradiation with gemcitabine had improved OS with increased, but acceptable, toxicity.

4 Induction Chemotherapy Followed by Chemoradiation

Given that a large percentage of patients who present with LAPC rapidly develop metastatic disease, investigators are pursuing a strategy of using induction chemotherapy to select the patients with localized disease. With this approach, the patients who do not progress after the several months of chemotherapy proceed to local therapy with chemoradiation. A retrospective study of 181 patients enrolled in phase II and III Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trials demonstrated that 29% had metastatic disease during the 3-month period of gemcitabine-based chemotherapy (Huguet et al. 2007). For the remaining patients, survival was significantly longer among those treated with chemoradiation (55 Gy with continuous infusion 5-FU) as compared to patients treated with additional chemotherapy (15.0 months vs. 11.7 months, $p = 0.0009$). Although this strategy has yet to be validated in a prospective randomized phase III trial, it provides support for the use of consolidative chemoradiation after 3 months of induction chemotherapy in those patients with localized disease.

Based on these findings, the GERCOR group designed the LAP 07 study where 442 patients with LAPC were initially randomized to gemcitabine or gemcitabine plus erlotinib (Hammel et al. 2013). The 269 patients (61%) without disease progression after 4 months of chemotherapy were subsequently randomized to chemoradiation or 2 months of additional chemotherapy. With a median follow-up of 36 months, there was no statistically significant difference in overall survival between the arms (16.4 vs. 15.2 months in the chemotherapy-alone and chemoradiation arms, respectively). Unquestionably, the results of the LAP 07 trial have further confused the question of chemoradiation for the treatment of LAPC.

5 Controversies Regarding Local Therapy for LAPC

The rationale for delivering induction chemotherapy followed by chemoradiation to patients with LAPC is compelling, as these patients have the need for both distant and local control. While induction chemotherapy aims to clear micrometastatic disease in a high-risk population, chemoradiation is delivered with the goal of tumor downstaging to increase the chances of curative resection. However, this strategy has yet to be validated in a prospective randomized phase III trial. In fact, the LAP 07 study showed no statistically significant difference in overall survival between the induction chemotherapy followed by chemoradiation and the chemotherapy-alone arms. Given the randomized data supporting chemotherapy alone, how can one still argue for the use of chemoradiation?

A recent study by Iacobuzio-Donahue et al. recognized SMAD4, a tumor suppressor, as a possible predictor of local versus distant progression (Iacobuzio-Donahue et al. 2009). In this series, rapid autopsies were performed on 76 patients with pancreatic cancer. Patterns of failure (locally destructive vs. metastatic) and status of several genes were correlated. At autopsy, 30% of patients had locally destructive pancreatic cancer, and 70% had widespread metastatic disease. Although these differing patterns of failure were unrelated to clinical stage at initial pre-

sentation, treatment history, or histopathologic features, the investigators found a marked association between SMAD4 status and patterns of failure. Patients with intact SMAD4 expression were considerably more likely to have locally destructive disease as compared to those with loss of immunolabeling ($p = 0.007$).

The relationship between SMAD4 and pattern of disease progression has been confirmed at the M.D. Anderson Cancer Center in a phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for LAPC (Crane et al. 2011). In the study, 11 of the 15 patients (73.3%) with intact SMAD4 expression exhibited a local pattern of progression, whereas 10 of the 14 patients (71.4%) with SMAD4 loss displayed a distant pattern of spread ($p = 0.016$). Taken together, these studies suggest that identification of patients with intact SMAD4 at initial diagnosis might help identify patients who would benefit from aggressive local therapy.

In addition to the notion that there may be a subgroup of patients with SMAD4-intact cancer who can benefit from local therapy, one must also consider an important limitation of the LAP 07 study—gemcitabine as the choice of chemotherapy. With a superior regimen such as FOLFIRINOX, which has been studied in the metastatic setting, a benefit may have been detected with chemoradiation after improved systemic control. Furthermore, it is possible that with this more active regimen, tumor downstaging may be significant enough to increase the chances of surgical resection. This is being studied by the Radiation Therapy Oncology Group (RTOG) 1201, a phase II randomized trial of high versus standard intensity local or systemic therapy for LAPC. In the study, patients will undergo SMAD4 testing and will then be randomized to one of the three arms: (1) gemcitabine for 12 weeks followed by intensity-modulated radiation therapy to 63 Gy, given with concurrent capecitabine; (2) gemcitabine for 12 weeks followed by three-dimensional conformal radiation therapy to 50.4 Gy with concurrent capecitabine; or (3) FOLFIRINOX for 12 weeks followed by three-dimensional conformal radiation therapy to 50.4 Gy with concurrent capecitabine. Likewise, in the ALLIANCE/ECOG phase II trial, patients will receive eight cycles of FOLFIRINOX, and will then be randomized to an additional four cycles of FOLFIRINOX or chemoradiation with concurrent capecitabine. We eagerly await the results of these studies particularly with regard to subgroups of patients that may benefit from chemoradiation. Until then, based on the LAP 07 trial, we judge that chemotherapy alone is a reasonable option for patients responding to systemic therapy. However, we favor consolidative chemoradiation to optimize local control and surgical resectability for those patients with localized disease who have difficulty tolerating chemotherapy, patients suffering from local progression, or patients who may be candidates for surgical resection.

6 Stereotactic Body Radiation Therapy (SBRT) in Locally Advanced Pancreatic Cancer

Although neoadjuvant chemoradiation has many potential benefits, the standard regimen consists daily treatments over a 6-week period. This puts a substantial drain on ill patients with life expectancies on the order of 1 year. In addition, it delays the possibility of surgery, the only potentially curative procedure for these patients. SBRT allows for the delivery of chemoradiation over the course of 1 week, thereby reducing the delay to surgery and decreasing the burden of long radiation schedules.

SBRT has been studied in several of clinical trials as an alternative treatment for the management of locally advanced pancreatic cancer. However, the advantage of SBRT remains unclear since it may not improve survival and may be associated with significant toxicity as reported in selected studies (Koong et al. 2005; Hoyer et al. 2005; Chang et al. 2009; Schellenberg et al. 2008; Crane and Willett 2009; Mahadevan et al. 2010; Didolkar et al. 2010). For example, one phase II study of SBRT for locally advanced pancreatic cancer included 22 patients who received 45 Gy in three fractions over 5–10 days (Hoyer et al. 2005). SBRT

was associated with poor outcome and pronounced acute toxicity, with worsening performance status, nausea, and pain. In addition, four patients developed severe gastric or duodenal mucositis or ulceration, and one patient experienced a nonfatal gastric perforation. In another study of 77 patients (81% with locally advanced and 19% with metastatic disease) undergoing a single fraction of SBRT with 25 Gy (Chang et al. 2009), the overall survival rates at 6 and 12 months were 56% and 21%, respectively. The 6- and 12-month rates of grade ≥2 late toxicity (predominantly mucosal) were 11% and 25%, respectively. In another trial of 16 patients receiving SBRT (25 Gy in 1 fraction) in between cycles 1 and 2 of gemcitabine chemotherapy, late gastrointestinal toxicity was even more common, with 5 grade 2 ulcers, 1 grade 2 duodenal stenosis, and 1 grade 4 duodenal perforation (Schellenberg et al. 2008).

However, more encouraging results have been described in other studies using reduced treatment fields, more conformal methods, and more than one fraction (Mahadevan et al. 2011; Chuong et al. 2013; Schellenberg et al. 2011; Polistina et al. 2010). For instance, one single-institution retrospective series of 73 patients with locally advanced or borderline resectable pancreatic cancer treated with induction chemotherapy followed by SBRT (5 fractions of 7–10 Gy each) (Chuong et al. 2013) had more promising outcomes. Of the 57 patients with borderline resectable disease, 32 went on to have surgery and 31 had R0 resections. Median overall survival was 16.4 and 15 months for the borderline and initially unresectable patients, respectively. The 1-year local control rate for patients who did not proceed to surgery was 81%. Moreover, there was no grade ≥3 acute toxicity and only 5% of patients experienced grade ≥3 late toxicity. A prospective Italian study of 23 patients with locally advanced pancreatic cancer received SBRT (30 Gy in 3 fractions) and gemcitabine chemotherapy (Polistina et al. 2010). There were 14 partial and 2 complete responses. In addition, two patients proceeded to surgery. Median survival was 10.6 months and no grade ≥2 acute or late toxicities were reported.

Notwithstanding these promising results, and that it is undoubtedly preferable for patients to undergo treatments over a 1- rather than 6-week period, the data are not conclusive and there remains uncertainty regarding the possibility for toxicity. Until evidence from randomized trials comparing SBRT to conventional chemoradiation is reported, the role of SBRT in the treatment of locally advanced pancreatic cancer remains unclear. Therefore, we recommend that patients with pancreatic cancer undergo SBRT within the setting of a clinical trial.

7 The Role of Adjuvant Chemoradiation for Resectable Pancreatic Cancer

The use of adjuvant chemoradiation for patients with resected pancreatic cancer represents one of the most passionately debated topics within the field of gastrointestinal oncology. Resection remains the only potentially curative procedure for pancreatic adenocarcinoma. Nonetheless, the 5-year survival rate in patients undergoing surgery is less than 20% (Nitecki et al. 1995; Piorkowski et al. 1982; Gudjonsson 1987). Local-regional relapse (50–85%) and metastatic disease both account for the pattern of failure (Tepper et al. 1976; Kalser and Ellenberg 1985). The goal of adjuvant treatment is to prevent recurrence and increase survival. However, the data surrounding the utility of adjuvant chemoradiation is mixed.

Several trials support the role of adjuvant chemoradiation. In a randomized trial of 21 patients sponsored by GITSG, individuals were randomized to either surgery alone or adjuvant 5-FU chemoradiation followed by additional 5-FU. Patients who received adjuvant treatment had significantly improved median and 5-year overall survival rates as compared to those undergoing surgery alone (21 vs. 11 months and 5% vs. 5%, respectively, $p = 0.03$) (Kalser and Ellenberg 1985). In a similarly designed study, the EORTC randomized 114 patients to surgery alone or adjuvant radiation (40 Gy split course) with concur-

rent 5-FU (25 mg/kg per day by continuous infusion). Although not statistically significant, adjuvant chemoradiation was associated with a trend toward improvement in median survival and 2-year survival (34% vs. 26%, respectively, $p = 0.099$) (Klinkenbijl et al. 1999).

Despite these favorable results, the benefit of adjuvant radiation remains questionable. The European Study Group for Pancreatic Cancer-1 (ESPAC-1) trial was a phase III trial that randomized 541 patients to surgery alone or adjuvant treatment with six cycles of chemotherapy alone, chemoradiation alone, or chemoradiation followed by six cycles of chemotherapy. Concurrent chemotherapy consisted of bolus 5-FU and leucovorin and adjuvant chemotherapy consisted of 5-FU. Radiation was delivered AP/PA 40 Gy split course, although up to 60 Gy could be delivered. While the trial showed a benefit to chemotherapy (median survival 20 vs. 14 months for patients receiving and not receiving chemotherapy, respectively), chemoradiation was associated with decreased survival (15 vs. 16 months for patients undergoing chemoradiation and no chemoradiation, respectively) (Neoptolemos et al. 2001; Neoptolemos et al. 2004). However, the results of this trial are controversial because of concerns regarding trial design and radiation technique (Abrams et al. 2001).

The RTOG 9704 trial sought to determine whether the addition of gemcitabine to 5-FU-based chemoradiation improved survival for patients with resected pancreatic adenocarcinoma. After surgery, 451 patients were randomized to either continuous-infusion 5-FU or gemcitabine before and after chemoradiation (Regine et al. 2008). Chemoradiation was the same for all patients and consisted of 50.4 Gy in daily fractions of 1.8 Gy with continuous-infusion 5-FU. Although there were no differences in overall survival when taking into account the entire cohort, patients with pancreatic head cancers ($n = 381$) in the gemcitabine arm had a trend toward improved survival as compared to those in the 5-FU arm (median and 3-year survival of 20.5 months and 31% vs. 16.9 months and 22%, respectively, $p = 0.09$). In addition, pretreatment CA19-9 level > 90 IU/L strongly predicted survival.

Building on the results from RTOG 9704, RTOG 0848 is a randomized trial to determine whether the addition of erlotinib to adjuvant gemcitabine improves survival as compared to gemcitabine alone after resection of head of pancreas adenocarcinoma (Regine et al. 2008). In addition, it also seeks to determine whether concurrent chemoradiation with 5-FU following adjuvant gemcitabine-based chemotherapy improves survival. We hope that trial will conclusively show that adjuvant radiation with concurrent 5-FU improves survival for patients with resected head of pancreas adenocarcinoma who do not progress after adjuvant gemcitabine-based chemotherapy.

Conclusion

The role of radiation therapy in the treatment for pancreatic cancer is currently controversial. Recent advancements in systemic therapy, including establishment of gemcitabine/abraxane and FOLFIRINOX chemotherapy in the localized setting, may allow for improved systemic disease control. With improvement in systemic therapies, local control may potentially be more meaningful endpoint. There are numerous ongoing studies, including RTOG 0848, that hopefully will answer the question of the benefit of radiation therapy in the upcoming years.

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Controversies in Radiotherapy for Hepatocellular Carcinoma

Guo-Liang Jiang and Zheng Wang

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Abstract

Radiation therapy for liver carcinomas has been used in some hospitals in North America and Europe, but widely in Asia. However, the role of radiation therapy in the management of liver carcinoma has not been recognized in liver cancer society, especially in North America and Europe. The modern radiation techniques, 3-dimensional radiation therapy, intensity-modulated radiation therapy, stereotactic body radiotherapy, and proton and carbon ion beam radiation therapy have yielded very encouraging outcome. Recently, the role of radiation therapy just started to be recognized by NCCN guideline.

In the radiation therapy society, there were controversies regarding the radiation techniques: (1) What was the optimal management to control target motion, especially for beam scanning delivery in proton and carbon ion therapy? (2) What were the optimal radiation fractionation and total dose for hypofractionated or stereotactic body radiation therapy? (3) What were the normal liver tolerances for the livers with different degrees of hepatic cirrhosis, when different irradiation fractionations and total doses were applied? (4) What were the appropriate indications for different radiation techniques?

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1 Introduction

Liver cancer is one of the leading cancer-related deaths globally. The incidence and mortality of liver cancer, respectively, ranked the sixth and the fourth places in the world. The estimated number of new liver cancer patients is 841,080, and the death is 781,631 patients in 2018 (Bray et al. 2018). In China the liver cancer incidence ranked the fourth place in cancer incidence and the third place in mortality according to the recent epidemiological investigation (Chen et al. 2016). Among liver cancers hepatocellular carcinoma (HCC) accounts for 85%, which results from hepatitis B or C virus-induced hepatic cirrhosis. Although HCC could be detected at early stages by alpha fetal protein (AFP), 60–70% of HCC is diagnosed at late stages in China.

The standard care of liver cancers is surgery, but only around 25% of liver cancer cases are candidates for surgery when diagnosed. The majority of liver cancers are either technically unresectable due to the locally advanced or medically inoperable due to poor hepatic functions, comorbidity, or contraindications for anesthesia. Therefore other alternative modalities play important roles in the management of liver cancers. However, for early stages of HCC, even after surgery the survivals are not satisfactory with 5-year survivals from 60% to 70%.

Currently, it has gradually been recognized the role of radiotherapy (RT) in the management of liver cancers since 1990s, when the modern RT technique of 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) was used in clinical RT practice. In the past two decades the clinical experience in RT for liver cancers has been accumulated, but not in a mature stage. There are controversies in the application of RT for liver cancers, and much room needs to be explored.

This chapter is mainly focusing on HCC and discusses the controversies based on BCLC stage proposed by Barcelona-Clinic Liver Cancer Group in 1999.

2 The Role of RT in the Management of HCC

2.1 BCLC Stage 0 and Stage A

BCLC stage 0 is the very early stage with single nodule of <2 cm in diameter, or carcinoma in situ, and with hepatic function of Child-Pugh A and performance status (PS) 0; and BCLC stage A is early stage with single or 3 nodules of ≤3 cm and Child-Pugh A-B and PS 0.

The flowchart of BCLC/American Association for Study of Liver Disease (AASLD) has been widely used in the world (Santambrogio et al. 2013; Kim et al. 2011). In this flowchart, for the early stages, surgical resection, liver transplantation, or percutaneous ethanol injection (PEI)/radiofrequency ablation (RFA) was the recommended the standard care. There was even no mention for the role of RT in the management of early stages of HCC. As the same as in AASLD flowchart, there was no role for RT in the guidelines of EORTC (Management of hepatocellular carcinoma, European Association for the Study of the Liver 2012) and ESMO–ESDO. However, there was a short remark about external RT, but the level of evidence and the grade of recommendation of 3C, which had the poorest evidence and the weakest recommendation. However, the role of internal RT was above the external RT with 2B of evidence level and recommendation grade (Verslype et al. 2012). Although those flowcharts were proposed to be further improved (Livraghi et al. 2010), EORTC stated it clear that "the benefits of external three-dimensional conformal radiotherapy have only been tested in uncontrolled investigations. There is no scientific evidence to recommend these therapies as primary treatments of HCC and further research testing modern approaches is encouraged."

NCCN guideline has been widely used globally. In 2017 NCCN guideline of HCC for BCLC stage 0 and A (T1N0M0) (www.nccn.org), the treatment of choice was surgery or liver

transplantation. For patients of BCLC stage 0 and A, who are not fit for surgery or ineligible for liver transplantation, the treatments recommended are locoregional therapy, which includes ablation by RFA, PEI, arterially directed therapies [trans-artery chemoembolization (TACE) and radioembolization (RE)], and external beam radiation therapy (EBRT) (conformal or stereotactic). Although EBRT has been listed as one of the options for locoregional therapies, the evidence is listed as the category 2B, which means lower level evidence. In contrast, ablation and arterially directed therapy were listed as the evidence of category 2, which means the uniform NCCN consensus. In other words, RT was not the uniform consensus in NCCN panel members, and the role of RT was inferior to ablation and arterial therapy. Nevertheless, it was changed that RT was proposed as one of the treatment choices for BCLC 0-1 with the evidence of 2A in 2018 NCCN guideline. It implies that liver cancer society in North America started to recognize the role of RT in the management of HCC.

Of course, for BCLC stage 0 and A, the surgical resection is believed to be the only modality to cure HCC, and yields the best survivals among all the treatments available so far. However, the candidates for surgery are limited by surgical contraindications due to the cardiovascular comorbidities, poor hepatic function, or patient refusal. For liver transplantation, it is a promising choice for HCC as it could eradicate HCC and its essential cause, cirrhotic liver, but because of shortage of the donor it could not be widely used. However, BCLC flowchart did not define what the treatment choice was for them.

In Chinese guideline for HCC external RT with 3D-CRT and IMRT was recommended for those with early stages of HCC, who were not suitable to surgery (Chinese Ministry of Health 2011; Chinese Society of Clinical Oncology 2018). The significantly different attitude to RT in China, and also in Asia, was due to that a large population of HCC had been treated by RT, and the outcome was encouraging.

In spite of not being recognized by the liver society in North America and Europe 3D-CRT and IMRT, and lately most advanced RT techniques, like stereotactic body radiotherapy (SBRT), stereotactic ablative body radiotherapy (SABR), and proton and heavy ion RT, have been gradually used in Asia since 1990. At the early time only locally advanced HCC was irradiated, and gradually for early-stage HCC. The outcomes were very encouraging.

2.1.1 3D-CRT/IMRT

3D-CRT/IMRT was innovated in 1990, which could deliver high dose to tumor and meantime spare adjacent organs at risk (OAR). Since then this technique has been used to treat HCC, mainly for those HCC unfit to surgery. In early 2000, conventional fractionation with 2 Gy per fraction and total doses from 30 Gy to 60 Gy were applied for 3D-CRT/IMRT alone, or combined with TACE. The outcomes were very good with the median survival time (MST) of 10–25 months, and 1-year overall survival (OS) of 47–93% and 3-year OS of 22–35% (Table 1).

2.1.2 SBRT/SABR

SBRT/SART was invented over a decade ago. The mechanism of SBRT/SABR is multiple X-ray beams focused at the center of tumor and delivered at very high doses to tumor while low dose, but large volume, to the normal organs adjacent to it.

Princes Margaret Hospital reported 102 patients treated by SBRT of 24–54 Gy in six fractions. All patients had Child-Pugh A disease and >700 mL of non-HCC liver. The associated liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol related in 25%, others in 14%, and none in 7%. TNM stage was stage III in 66%, and 61% had multiple lesions. The median gross tumor volume was 117 mL. Tumor vascular thrombosis (TVT) was present in 55%, and extrahepatic disease was present in 12%. Toxicity of ≥grade 3 was seen in 30% of patients. Local control rate at 1 year was 87%. Seven patients (two

Table 1 Outcome of 3D-CRT/IMRT by conventional fractionation irradiation in hepatocellular carcinoma

Study	Patient No.	Treatment	Dose (Gy)	MST (mo)	OS
Seong (1999)	30	3D-CRT + TACE	44 (2 Gy/fx)	17	3-year 22.2%
Seong (2000)	27	3D-CRT	40–60 (2 Gy/fx)	14	3-year 21.4%
Park (2002)	158	3D-CRT	40–60 (1.8 Gy/fx)	10	2-year 19.9%
Liu (2004)	44	3D-CRT	39.6–60 (1.8 Gy/fx)	15.2	1-year 60% 3-year 32%
Seong (2003)	158	3D-CRT + TACE	25.2–50.0 (1.8 Gy/fx)	16	1-year 59% 5-year 9%
Guo (2003)	76	3D-CRT + TACE	30–50 (1.8–2.0 Gy/fx)	19	1-year 64% 5-year 19%
Zeng (2004)	54	3D-CRT + TACE	36–60 (2 Gy/fx)	20	1-year 72% 3-year 24%
Park (2005)	59	3D-CRT	30–55 (2–3 Gy/fx)	10	1-year 47% 2-year 27%
Zhou (2007)	50	3D-CRT + TACE	30–54 (2 Gy/fx)	17	3-year 26%
Hsu (2006)	121	3D-CRT	45–75 (1.5 Gy/fx, 2 fx/d)	19	2-year 44.6%
Kim (2006)	70	3D-CRT	44–54 (2–3 Gy/fx)	18	2-year 17.6%
Mornex (2006)	27	3D-CRT	66 (2 Gy/fx)	NA	NA
Ren (2011)	40	3D-CRT + TACE	42–62 (2 Gy/fx)	–	LC 2-year 93% OS 2-year 62%

3D-CRT 3-dimensional conformal radiation therapy, *d* day, *fx* fraction, *IMRT* intensity-modulated radiation therapy, *LC* local control, *mo* month, *MST* median survival time, *OS* overall survival, *TACE* trans-catheter artery chemotherapy and embolization, *wk* week, *yr* year

with TVT) died possibly related to treatment 1.1–7.7 months after SBRT. Median OS was 17.0 months. Authors thought that their results provided strong rationale for a randomized trial to test the role of SBRT in HCC (Bujold et al. 2013).

Kang reported 50 inoperable HCC of a greatest tumor dimension of 2.9 cm (1.3–7.8 cm), and incomplete response after TACE. Moreover, five patients had portal vein tumor thrombosis (PVTT). SBRT was used with the doses from 42 Gy to 60 Gy in three fractions (median, 57 Gy). The 2-year LC rate was 94.6%; OS 68.7%; and PFS 33.8%. Three patients (6.4%) experienced grade 3 gastrointestinal toxicity, and two patients (4.3%) grade 4 gastric ulcer perforation (Kang et al. 2012).

Sixty-three untreated solitary HCC patients were irradiated by SABR with doses of 35–40 Gy in five fractions in Takeda's report. Twenty patients were treated with only SABR, and 43 patients with SABR after TACE. The 1-year, 2-year, and 3-year LC rates were 100%, 95%, and 92%; the intrahepatic recurrence-free rates were 76%, 55%, and 36%; and the OS were 100%, 87%, and 73%, respectively. The acute, subacute, and chronic phases of ≥grade 3 were observed in 10, 9, and 13 patients, respectively. Authors concluded that SABR was safe and an alternative for HCC unfit for surgery or ablation (Takeda et al. 2014).

Sanuki reported a retrospective study on HCC treated by SBRT for the curative intent. HCC with a single (either solitary or recurrent) lesion; unfeasible, difficult, or refusal to surgery or percutaneous ablative therapies; Child-Pugh A or B; and tumors ≤5 cm were selected for the analysis. A total of 185 patients were collected (48 in 35 Gy group, and 137 in 40 Gy group). The 3-year LC and OS were 91% and 70%, respectively. Acute toxicities of ≥grade 3 were observed in 24 cases (13.0%), and 19 cases (10.3%). Grade 5 of liver failure occurred in two patients in the 35 Gy group (Sanuki et al. 2014).

Table 2 summarizes the outcome of early stage of liver cancers, mainly HCC treated by SBRT/SABR published since 2000. The fraction size was from 4 Gy to around 10 Gy. The LC ranged from 66% to 75% at 2 years, and 21% to 75% at 2 years and 59% to 73% at 3 years,

Table 2 Outcome of liver cancers treated by hypofractionated RT or SBRT/SARB

	No. of pts	Tumor size	Dose	LC	OS
Wu (2004)	94	10.7 cm	48–60 Gy (4–8 Gy/fx)	93% (1 year)	26% (3 years)
Liang (2005)	128	459 cm^3	40–60 Gy (4–8 Gy/fx)	–	33% (3 years)
Choi (2008)	31	25 mL	30–39 Gy/3 fx	95% (1 year)	52% (2 years)
Kwon (2010)	42	15 mL	30–39 Gy/3 fx	68% (3 years)	59% (3 years)
Seo (2010)	38	41 mL	33–57 Gy/3–4 fx	66% (2 years)	61% (2 years)
Andolino (2011)	60	3.2 cm	CP-A 44 Gy/3 fx CP-B 40 Gy/5 fx	90% (2 years)	67% (2 years)
Kang (2012)	50	2.9 cm	42–60/3 fx	94.6% (2 years)	68.7% (2 years)
Huang (2012)	36	4.4 cm	25–48 Gy/4–5 fx	75% (2 years)	64% (2 years)
Dewas (2012)	153	3.3 cm	45 Gy/3 fx	84% (1 year)	75% (2 years)
Ibarra (2012)	32	HCC 334 mL CCC 80 mL	HCC 18–26 Gy/10 fx ICC 22–30 Gy/15 fx	75% (2 years)	55% (2 years)
Bujold (2013)	102	7.2 cm	24–54 Gy/16 fx	87% (1 year)	MST 17 months
Bae (2013)	35	131 mL	30–60 Gy/3–5 fx	51% (3 years)	21% (2 years)
Takeda (2014)	63		35–40 Gy/5 fx	92% (3 years)	73% (3 years)
Sanuki (2014)	185	8 mL	CP-A 40 Gy/5 fx CP-B 35 Gy/5 fx	91% (3 years)	70% (3 years)
Lazarev (2018)	53	Central	BED10 = 72 Gy	87.9% (2 years)	39% (2 years)

CP-A Child-Pugh A, *CP-B* Child-Pugh B, *fx* fraction, *HCC* hepatocellular carcinoma, *ICC* intrahepatic cholangiocellular carcinoma, *LC* local control rate, *OS* overall survival rate, SABR stereotactic ablative body radiotherapy, *SBRT* stereotactic body radiotherapy

respectively. The advantages of RT over PEI and RF include the following: (1) Up to 5 cm diameter lesion could be effectively controlled by RT. (2) Lesions located adjacent to large vessels and biliary ducts are not contraindications. (3) RT is totally noninvasive. The SBRT/SARB data were mainly from retrospective studies, and the follow-up time was not long enough, but the benefit from SBRT/SARB is significant.

2.1.3 Proton and Heavy Ion RT

In the past two decades, particle ion RT, predominantly proton and carbon ion, has been adopted in treating HCC. Particle ion RT is the latest innovation in RT technology, the cutting-edge technique. Because of the physical characteristic of Bragg peak dose distribution very high RT doses could be delivered to tumors, and meantime spare the adjacent normal organs significantly. Moreover, the carbon ion, as high linear energy transfer (LET) beam, facilitates with high biological effect, which could effectively kill those photon-resistant tumor cells, like hypoxic cells in HCC. Thus, particle ion RT has great potential to cure HCC.

Chiba in Tsukuba University, Japan, first reported the outcome of 162 patients with HCC (192 lesions) treated by proton beam RT from 1985 to 1998. All patients were medically inoperable or technically unresectable due to hepatic dysfunction, multiple tumors, and recurrence after surgical resection, or concomitant illnesses. The median diameter of tumor was 3.8 cm (1.5–14.5 cm). Twenty-five out of 162 patients had portal vein tumor thrombosis (PVTT). The hepatic background was Child-Pugh A of 82 cases (50.6%), Child-Pugh B of 62 cases (38.3%), and Child-Pugh C of 10 cases (6.2%). The median total dose of proton irradiation was 72 GyE (Gy equivalent to ^{60}Co) in 16 fractions over 29 days. The fraction sizes were from 4.5 GyE to 5 GyE and the total doses from 50 GyE to 72 GyE. The local control rate at 5 years was 86.9% for 192 tumors among the 162 patients. The 5-year OS was 23.5%. The late toxicity of ≥G2 occurred in 3% of patients. This was the first paper in the literature to show that proton beam RT was effective in treating HCC, and demonstrated that it's safe and well tolerable. They also proposed that proton RT was a useful

treatment for either cure or palliation for HCC, irrespective of tumor size, tumor location, presence of vascular invasion, impaired hepatic functions, or coexisting intercurrent diseases (Chiba et al. 2005).

Tsukuba University continued proton RT. From 2001 to 2007, they treated a total of 318 HCC. There were 234 patients (73.6%) of Child-Pugh A, 77 (24.2%) of Child-Pugh B, 7 (2.2%) of Child-Pugh C, 150 (47.2%) of T1, 107 (33.6%) of T2, and 61 (19.2%) of T3. A total dose of 77 GyE in 35 fractions was used for tumors within 2 cm of the digestive organ, 72.6 GyE in 22 fractions was used for tumors within 2 cm of the porta hepatis, and 66 GyE in 10 fractions was delivered to peripheral tumors >2 cm from both the gastrointestinal tract and the porta hepatis. OS rates for all 318 patients were 89.5%, 64.7%, and 44.6% at 1 year, 3 years, and 5 years, respectively. Five-year LC rate was 83.3%. No treatment-related death was observed. No patients discontinued the treatment because of liver toxicity. Only four patients developed radiation-related gastrointestinal toxicities (three with grade 2 GI ulcers and one with grade 3 hemorrhage of the colon, all of which were successfully treated by surgery) (Nakayama et al. 2009).

National Cancer Center in Japan treated 30 old patients with HCC (median age of 70 years) with median diameter of 45 mm (25–82). Twenty patients were associated with Child-Pugh A, and ten patients class B. Proton of 76 GyE in 20 fractions and 5 weeks was delivered. After a median follow-up period of 31 months, only one patient experienced recurrence of the primary tumor, and 2-year actuarial local progression-free rate was 96% and 2-year OS was 66%. Acute reactions of proton RT were well tolerated. Four patients died of hepatic insufficiency without tumor recurrence at 6–9 months. Three of these four patients had pretreatment indocyanine green retention rate at 15 min of more than 50% (Kawashima et al. 2005).

Recently, a multi-institutional phase II study was published in the USA, which included 44 patients of HCC and 37 with intrahepatic cholangiocellular carcinoma (ICC), all unresectable with a Child-Pugh score of A or B. The median maximum dimension was 5.0 cm (1.9–12.0 cm) for HCC patients and 6.0 cm (2.2–10.9) for ICC patients. Multiple tumors were present in 27.3% of HCC patients and in 12.8% of ICC patients. PVTT was present in 29.5% of HCC patients and in 28.2% of ICC. All received proton of 58.0 GyE in 15 fractions, for 3 weeks. The LC rate at 2 years was 94.8% for HCC and 94.1% for ICC. The OS rate at 2 years was 63.2% for HCC, and 46.5% for ICC (Hong et al. 2015).

University of Kobe treated HCC with proton or carbon beams. There were 242 HCC (with 278 tumors) irradiated with proton RT of 52.8–84.0 GyE in 4–38 fractions and 101 HCC (with 108 tumors) treated by carbon 52.8–76.0 GyE in 4–20 fractions. The 5-year LC and OS rates for all patients were 90.8% and 38.2%, respectively. The 5-year LC rates were 90.2% and 93%, and the 5-year OS were 38% and 36.3%, respectively, for proton and carbon ion. No patients died of treatment-related toxicities (Komatsu et al. 2011).

Table 3 summarizes the outcome of proton RT for liver cancers.

National Institute of Radiological Science (NIRS) is the first hospital to treat HCC with carbon ion. Kasuya recently reported a retrospective analysis of 124 HCC patients with a total of 133 lesions in NIRS. The fraction number was 12, 8, or 4 fractions with 4.5–13.2 GyE per fraction. The LC rates at 1 year, 3 years, and 5 years were 94.7%, 91.4%, and 90.0%, and OS at 1 year, 3 years, and 5 years were 90.3%, 50.0%, and 25.0%, respectively. The failure pattern was mainly in the liver outside of irradiated volume (77%), and out of liver (26%). There were no ≥3-point increase of Child-Pugh score observed (Kasuya et al. 2017). To shorten the treatment time NIRS further reduced the fraction number to two fractions with total doses of 32–45 GyE. Among 133 HCC treated there were 92% of Child-Pugh A patients and 8% Child-Pugh B, and 87% of UICC stages 1–2 and 23% of stages IIIA and IVA. The median maximum tumor diameter was 42 mm (14–140 mm). Acute toxicity was slight with only four cases of G3 hepatic toxicity and none of other G3 and G4–5 toxicity. So was the late toxicity. The LC rates were 98% and 90% at 1 year and 83% and 76% at

Table 3 Outcome of proton irradiation for hepatocellular carcinoma

Author	No. of pts	Dose	Toxicity	Efficacy
Chiba (2005)	162 (25 with PVTT)	Proton 72 GyE/16 fx (3.5–5 GyE/fx)	Late ≥G2, 3%	5-year OS 23.5% 5-year LC 86.9%
Nakayama (2009)	318	Proton 66 GyE/10 fx to 77.0 GyE/35 fx		OS: 1 year 89.5%, 3 years 64.7%; 5 years 44.6%; LC: 5 years 83.3%
Kawashima (2005)	30 (mean age of 70 years)	Proton 72 GyE/16 fx	Hepatic insufficiency (≤G3), 27%	2-year OS 66%, 2-year PFS 96%
Mizumoto (2011)	266	Proton 66–77 GyE/10–35 fx	*G* ≥3, 3%	OS: 1 year 87%, 3 years 61%, 5 years 48% (MST 4.2 years). LC: 1 year 98%, 3 years 87%, 5 years 81%
Bush (2011)	76	Proton 63 GyE/15 fx, 3 weeks	Acute toxicity: minimal	3-year PFS 60%; PFS: 36 months (30–42)
Komatsu (2011)	242	Proton 52.8–84.0 GyE/4–38 fx Carbon 52.8–76.0 GyE/4–20 fx		5-year LC 90.8%; 5-year OS 38.2%
Kim (2015a)	27	Proton 60 GyE/20 fx; 66 GyE/22 fx; 72 Gy/24 fx	No DLT (G3)	LPFS 3 years 79.9%, 5 years 63.9% OS 3 years 56.4%, 5 years 42.3%

DLT dose-limiting toxicity, *LPFS* local progression-free survival, *OS* overall survival, *PFS* progression-free survival, *PVTT* portal vein tumor thrombosis

3 years in the higher dose group (45 GyE) and the lower dose group (≦42.8 GyE), respectively. OS rates at 1 year were 95% and 96%, and 71% and 59% at 3 years in the higher dose group (45.0 GyE) and the lower dose group (≦42.8 GyE), respectively (Tsujii et al. 2014).

In 2015 Qi et al. did a meta-analysis to compare photon RT, SBRT, and charged particle RT (proton and heavy ion) in terms of toxicity and efficacy for HCC. It included 73 cohorts from 70 non-comparative observational studies. The study showed that OS in charged particle RT was higher than that in photon RT, but similar to that in SBRT. The RT toxicity was lower in charged particle RT than that in photon RT and SBRT (Qi et al. 2015).

Overall, proton and carbon ion RT yielded more promising outcome than photon RT and SBRT, especially less toxicity incidences.

2.1.4 Comments for the RT Role in BCLC Stage 0 and Stage A

Currently, surgery is the standard care for early stages of HCC, and 5-year OS was from 63.1% to 76.9%, which is the best among the all modalities available. The PEI and RFA have also been recommended as the options for early stage of HCC in most of the guidelines or consensus for HCC, although their efficacy is not as good as that in surgery (Table 4). However, those modalities have their limits. Surgery needs patients with good performance status and liver function reservation. PEI and RFA are preferred to treat small size of HCC, ideally <3 cm in diameter. Moreover, it was noticed that the recurrence at the tumor site after RFA increased with tumor size: 14% (<3 cm), 25% (3–5 cm), and 58% (>5 cm) (Mulier et al. 2005). In addition, the hepatic lesion location close to large vessels and bile ducts is the contraindication for RFA.

On the other hand, the new advanced RT techniques have shown the good LC and survivals, SBRT/SARB resulted in LC of 66–95% at 1 year, 51–92% at 3 years, and 59–73% at 5 years, respectively. Proton produces much better LC with 64.7–90.8% at 5 years, and OS of 64.7–83.3% at 3 years and 23.5–44.6% at 5 years, respectively. Carbon ion RT yielded even more promising results, and less irradiation-related toxicity. Those LC and OS were

Table 4 Outcome of RES, PEI, TACE, and RFA for early stages of hepatocellular carcinoma

Author	No. of pts	Tumor size (cm)	Treatment	Efficacy
Cho (2007)	116	≤233.1%	RES	OS: 1 year 94.8%, 3 years 76.5%, 5 years 65.6% DFS: 1 year 76.1%, 3 years 50.6%, 5 years 40.6%
	116	≤267.9%	PEI	OS: 1 year 95.7%, 3 years 73.5%, 5 years 49.3% DFS: 1 year 62.6%, 3 years 25.5%, 5 years 19.1%
Kagawa (2010)	62	≤5 cm	TACE + RFA	OS: 1 year 100%, 3 years 94.8%, 5 years 64.6% RFS: 1 year 64.5%, 3 years 40.1%, 5 years 18%
	55		RES	OS: 1 year 92.5%, 3 years 82.7%, 5 years 76.9% RFS: 1 year 75.6%, 3 years 41.1%, 5 years 36.4%
Nishikawa (2011)	69	≤3 cm	RES	OS: 1 year 100%, 3 years 81.4%, 5 years 74.6% RFS: 1 year 86.0%, 3 years 47.2%, 5 years 26.0%
	162		RFA	OS: 1 year 95.4%, 3 years 79.6%, 5 years 63.1% RFS: 1 year 82.0%, 3 years 38.3%, 5 years 18.0%
Guo (2013)	102	≤5 cm	RES	OS: 1 year 89.2%, 3 years 74.1%, 5 years 63.1% DFS: 1 year 59.8%, 3 years 42.4%, 5 years 40.8%
	94		RFA	OS: 1 year 94.7%, 3 years 74.7%, 5 years 49.8% DFS: 1 year 57.9%, 3 years 36.4%, 5 years 34%

RES resection, *PEI* percutaneous ethanol injection, *TACE* trans-artery chemoembolization, *RFA* radiofrequency ablation, *OS* overall survival, *RFS* relapse-free survival, *DFS* disease-free survival

comparable to those in PEI and RFA. In 2016 Wahl et al. did a comparison study between SBRT and RFA for early stages of HCC around 2 cm in diameter. They collected 161 patients treated by RFA, and 63 by SBR. OS rates at 1 year and 2 years were 75% and 53% after RFA, and 74% and 46% after SBRT, with no significant differences (Wahl et al. 2016).

In spite of lack of randomized studies, but large number of patients treated by RT, RT should have been proposed as one of the options for early-stage HCC. Actually, more attentions had been paid to RT recently. Klein and Dawson proposed that RT should be recommended to HCC BCLC stage 0-A, when they are not fit for surgery or PEI/RFA, and also as a bridge when the patients wait for liver transplantation (Klein and Dawson 2013). In 2016, Dhir listed the major treatment options available to patients with HCC, and added RT (conventional RT, SBRT, and proton) as a non-curative intent treatment (Dhir et al. 2016).

In 2014 American Society of Therapeutic Radiation Oncology (ASTRO) released model policies on proton RT, in which HCC was listed in Group 1 of malignancies for proton RT (ASTRO 2014). That means that radiation therapy society recognizes the role of proton RT in HCC.

Among the different RT techniques it was believed that conventional RT, SBRT, and particle RT yielded similar LC for tumor size of <5 cm in diameter, but proton and carbon ion RT can spare more normal liver, so more HCC patients would have chances to be irradiated, especially for tumors >5 cm in diameter, and deeply seated, like in hepatic hilar.

2.2 BCLC Stages B and C

For BCLC stages B and C TACE and sorafenib are the only treatments of choice in the majority of diagnosis and treatment guidelines for liver cancer. However, there are patients with PVTT and locoregional node metastases in BCLC stage C. For those patients, RT could also play a role of palliative treatment.

2.2.1 The Efficacy and Toxicity of RT for BCLC Stage B and Stage C

Kim and his colleagues have used IMRT to treat inoperable HCC (great vessel invasion or big size). The simultaneous integrated boost IMRT (SIB-IMRT) was employed for 53 patients. For 41 patients with tumor location of <1 cm to GI (low-dose fractionation, LD) 44 Gy in 22 fractions was delivered to clinical tumor volume

(CTV), which included the gross tumor and adjacent microinvasion, and simultaneously 55 Gy in 22 fractions, to gross tumor volume (GTV). For 12 patients with tumor away from GI (≥1 cm) (high-dose fraction, HD), total doses of 55 Gy in 22 fractions were given to CTV and 66 Gy to GTV. The toxicity was tolerable with no grade >3. The OS was 25.1 months, and the 2-year LPRS, RFS, and OS rates were 67.3%, 14.7%, and 54.7%, respectively. The HD group tended to have better 2-year LPFS (85.7% vs. 59%, $p = 0.119$), RFS (38.1% vs. 7.3%, $p = 0.063$), and OS (83.3% vs. 44.3%, $p = 0.037$) rates than the LD group (Kim et al. 2014). Later, Kim and his group continued their study, using the same SIB-RT technique, but delivered by proton. A total of 27 inoperable HCC had been treated with 60 GyE in 20 fractions to CTV and 72 Gy in 24 fractions to GTV. No dose-limiting toxicity (G3) was noticed. The LPFS and OS rates were 79.9% and 56.4% at 3 years, and 63.9% and 42.3% at 5 years, respectively (Kim et al. 2015a).

A prospective phase 2 multicenter trial of 3D-CRT was carried out in South Korea for unresectable HCC cases, who had viable tumor after TACE of no more than three courses. A total of 31 patients were enrolled. 3D-CRT was delivered at a median dose of 54 Gy by 1.8–2 Gy per fraction. The 2-year in-field LPFS, PFS, TTP, and OS rates were 45.2%, 29.0%, 36.6%, and 61.3%, respectively. Radiation-induced liver disease (RILD) was not observed. There were no treatment-related deaths or hepatic failure (Choi et al. 2014). Cho reported a total of 116 patients with locally advanced HCC treated by TACE + RT (67 patients) or sorafenib (49 patients). At baseline, the sorafenib group had more patients with a tumor size ≥10 cm, lymph node metastasis, and PVTT compared to the TACE + RT group. The OS in the TACE + RT group was significantly longer compared to the sorafenib group (14.1 vs. 3.3 months, $p < 0.001$). In the score-matched cohort, and TACE + RT group showed prolonged OS compared to the sorafenib group (6.7 vs. 3.1 months, $p < 0.001$). Multivariate analysis revealed that TACE + RT was the only independent prognostic factor associated with survival in the propensity score-matched cohort (HR = 0.172, $p < 0.001$). In 2015 a systematic review and a meta-analysis were published, which compared TACE alone to TACE plus RT for unresectable HCC, or with portal venous tumor thrombosis (PVTT) (Huo and Eslick 2015). A total of 25 trials (11 RCTs) including 2577 patients were collected. The analysis showed that patients receiving TACE plus RT showed significantly better survivals at 1, 2, 3, 4, and 5 years compared with TACE alone, although the incidence of gastroduodenal ulcers and hepatic injury was higher in patients with TACE plus RT than that in TACE alone.

Tang did a retrospective study of 371 patients with resectable HCC, but with PVTT. The patients were treated in two hospitals by surgical resection in one hospital (186 patients) or by 3D-CRT in the other hospital (185 patients). A total radiation dose of 30–52 Gy (median 40 Gy) was delivered by 3D-CRT to the tumor and PVTT. TACE was applied after surgery or 3D-CRT and then was repeated every 4–6 weeks. The median survival was 12.3 months for 3D-CRT and 10.0 months for surgery. The 1-, 2-, and 3-year OS rates were 51.6%, 28.4%, and 19.9% for 3D-CRT and 40.1%, 17.0%, and 13.6% for surgery, respectively ($p = 0.029$). Multivariate analysis showed that the extent of PVTT and mode of treatment were independent risk factors of OS. The most common death cause was the consequence of progressive intrahepatic disease (Tang et al. 2013).

Hou retrospectively collected 181 HCC with PVTT and/or inferior vena cava thrombosis (IVCTT), and those patients were irradiated by external RT with a median total dose of 50 Gy (30–60 Gy). The median OS was 10.2, 7.4, 17.4, and 8.5 months for patients with PVTT in portal vein (PV) branch, PV trunk, inferior vena cava (IVC), and PV plus IVC, respectively (Hou et al. 2012).

Kim did a single-center retrospective study which involved 557 patients with HCC with PVTT. They received TACE ($N = 295$), TACE and RT (TACE + RT) ($n = 196$), or sorafenib ($n = 66$). The TACE + RT group had longer median TTP and OS than the TACE-alone and sorafenib ($p < 0.001$). Multivariate analysis

revealed that TACE + RT was an independent predictor of favorable TTP and OS. In the matched cohort, the median TTP was significantly longer in TACE + RT than TACE alone (8.7 vs. 3.6 months, $p < 0.001$), and so were the OS (11.4 vs. 7.4 months, $p = 0.023$). In the matched 30 pairs of patients, TACE+RT yielded better TTP (5.1 vs. 1.6 months, $p < 0.001$) and OS (8.2 vs. 3.2 months, $p < 0.001$) than the sorafenib (Kim et al. 2015b).

Yoon analyzed 412 HCC patients with PVTT treated by TACE and 3D-CRT. Main or bilateral PVTT was observed in 200 (48.5%) patients. A median radiation dose of 40 Gy (21–60 Gy) was delivered in 2–5 Gy per fractions. CR was observed in 3.6% of patients and PR 24.3%. The progression-free rate was 85.6%. Median OS was 10.6 months, and the 1- and 2-year survival rates were 42.5% and 22.8%, respectively. G3-4 hepatic toxicity occurred in 41 patients (10.0%) during or 3 months after completion of radiotherapy, and G2-3 gastroduodenal complications in 15 patients (3.6%) (Yoon et al. 2012).

A randomized trial was carried out in South Korea with 90 HCC (Child-Pugh A, and median diameter of 9.7 cm) with portal vein invaded. They was evenly divided to sorafenib (400 mg bid) or TACE, every 6 weeks combined with RT of 45 Gy, in 2.5–3 Gy per fraction. Better outcomes were seen in TACE combined with RT, compared with sorafenib with 12-week PFS (86.7% vs. 34.3%, $p < 0.001$), 24-week overall respond rate (ORR) (33.3% vs. 2.2%, $p < 0.001$), median time to progression (mTTP) (31.0 vs. 11.7 weeks, $p < 0.001$), and median overall survival (mOS) (55 vs. 43 weeks, $p = 0.04$) (Yoon 2018). Therefore, for HCC with PVTT combined RT and TACE could be one option for BCLC B and C, besides sorafenib.

For BCLC stage C there were patients with metastases in lymph node, adrenal gland, bone, lung, and brain metastases, Chinese experience in treating them with RT also showed the palliative effect (Jiang and Zeng 2013).

2.2.2 Comments for the RT Role in BCLC Stage B and Stage C

All RT data shown above were from Asia, but they showed the promising local control and survivals and were superior to other treatment modalities, like TACE and sorafenib in terms of palliation. Sorafenib could be the treatment choice for BCLC stage C, although the palliative effect is very limited. One could ask why RT could not be one of the treatment options.

In the European guidelines for HCC, there was no role for RT for BCLC stage C at all. For NCCN guideline of hepatobiliary cancers the external RT was not strongly recommended to treat unresectable HCC until 2018 edition of NCCN. The recommendation level was raised to category 2A. However, ablation and arterially directed therapies were recommended much early as category 2A. Sorafenib efficacy was very limited, but the evidence was category 1.

In 2011, Chinese Ministry of Health issued a practice guideline of the diagnosis and treatment for liver cancer (Ministry of Health of the People's Republic of China 2011). RT was recommend for those patients with vascular invasion, or inadequate hepatic reserve. In addition, RT could be used as a palliative treatment for HCC with PVTT, or distant metastases to relieve pain. However, RT combined with other modalities, like TACE and sorafenib, is strongly recommended.

2.3 Summary of the Role of RT in the Management of HCC

As presented in the previous text, the modern RT techniques have shown their promising efficacies in the treatment for early-stage and locally advanced HCC. It is time to re-evaluate the role of RT in the management of HCC. However, it is a consensus that a clinical practice could be recommended in the diagnosis and treatment guidelines only after prospective randomized clinical trials have confirmed it. At present time the majority of RT data accumulated in the literature were retrospective or single-arm studies, and the follow-up time was not long enough. Nevertheless, the prospective randomized clinical trials cannot always be done in reality because of the patients' acceptance and financial obstacles. It is the task of RT society to accumulate a large number of patients treated

by RT, and repeat excellent outcome to convince liver cancer society to realize the role of RT in the management of HCC. Even the panel members for 2018 NCCN Guideline for Hepatobiliary Cancers had started to realize the important role of RT in the treatment of liver cancer. Therefore the evidence and consensus category of RT role for resectable, transplantable, and unresectable HCC was shifted from 2B in 2017 NCCN Guideline to 2A in 2018 edition. That meant that the panel members in North America uniformly believed that RT was appropriate. It is expected that the guidelines for liver cancers from big liver cancer societies in other continentals would change their attitude sooner and later.

3 Radiation Techniques

3.1 Target Moving Control

The target motion is a great challenge in liver cancer RT. The methods used to control the target motion include abdominal compression, active breath coordinator (ABC), and respiratory gating, like RPM from Varian and Enzai from Japan. It is evident that use of breath control management can reduce the dose to liver. As reported by Zhao (2008), compared to free breathing, ABC reduced the mean dose to normal liver (MDTNL) (16.9 Gy vs. 14.3 Gy), PTV (529 cm^3 vs. 781 cm^3), and V23 (45% vs. 30%). The predicted incidence of RILD by Lyman model was also decreased (1% vs. 2.5%). In Gong's dosimetric study when RapidArc was used, MDTNL, normal liver V10, V20, V30, and V40 were remarkably lower (10.23 Gy, 35%, 16%, 8%, and 5% at the end of exhale and 9.23 Gy, 32%, 16%, 8%, and 5% at the end of inhale, respectively) than 13.12 Gy, 46%, 24%, 13%, and 8% at free breathing (Gong et al. 2012). When the respiratory gating is used the beam on time is always chosen at the end of exhale. Therefore, both ABC and gating could decrease the normal liver dose and can be used for photon RT. There was no debate for breath control management, but the techniques need further improvement.

However, the use of respiratory gating was questioned for proton and heavy ion RT because the residual motion in the gating window would induce the changes of tissue density along the beam pass way so as to produce the range uncertainty, resulting in Bragg peak deposited in wrong position. Besides, the interplay effect produces another dose uncertainty for the moving target when beam scanning technique is used to deliver dose. To deal with the interplay effect re-scanning technique is used, but the interplay effect could not be get rid of totally.

3.2 RT Dose and Fractionation

As listed in Tables 1–3, the fraction size, fraction number, and total dose were quite various. For 3D-CRT and IMRT the conventional fractionation was used with 2 Gy per fraction and the total dose, up to 66 Gy, For SBRT/SARB large fraction size ranging from 7 Gy to 15 Gy per fraction was used, and the fraction number ranged from three to ten fractions. For proton RT, large fraction size had also been applied. However, Tsukuba experience was of reference value. Their dose fractionation was based on the tumor locations: 6.6 GyE per fraction for 10 fractions for peripheral tumor, 3.3 GyE per fraction for 22 fractions for tumors close to portal hepatis (<2 cm), and 2 GyE per fraction for 37 fractions for tumor close to gastrointestinal tract (<2 cm).

For carbon ion RT, NIRS has done a series of clinical trials on HCC with gradual reduction of fraction numbers, from 15 fractions to 2 fractions to find the most appropriate fractionation. Finally, 38.8–52.8 GyE was delivered in 2 fractions.

HCC was thought to be moderately radiosensitive, like epithelial carcinomas. However, there have not been widely accepted optimal dose fractionations for conventional or hypofractionated RT. It is the trend to reduce fraction number and shorten the irradiation period by increase of fraction size, like SBRT. By this way the tumoricidal effect would be enhanced because of the stronger tumor killing and less tumor repopulation. Nevertheless, the optimal RT fractionation has not concluded yet, but it is believed that the

biological effect dose (BED10) of >100 Gy estimated by L-O modal was necessary to control HCC. The recommended dose fractionation was 8–10 Gy per fraction for five fractions, when SBRT was used (Ohri et al. 2018). Therefore, the optimal RT fractionation has not been established yet.

3.3 The Normal Liver Irradiation Tolerance

The normal liver tolerance is strongly dependent on the fraction size, total dose, irradiated normal liver volume, and particularly hepatic underline disease, like hepatitis-induced cirrhosis. It is consensus that the RT tolerance for the liver with hepatic cirrhosis is much worse than that for liver with healthy background. Therefore, it should be always kept in mind when considering liver RT tolerance.

For the conventional fractionation, like 2 Gy per fraction, it was proposed as early as in 1965 by Ingold (1965) and in 1991 by Emami. The recommended liver tolerance doses were 30 Gy, 45 Gy, and 55 Gy for entire, two-thirds, and one-third of liver irradiation (Emami et al. 1991). These tolerances have been widely accepted and used as the dose constraint for liver RT. However this tolerance derived from photon irradiation for liver cancers, majority of which were metastatic liver cancers from gastric and colon cancers, and small percentage of patients were HCC. However, the live background in metastatic liver cancer patients was healthy, whereas predominant HCC patients are associated with hepatitis B- and C-induced hepatic cirrhosis. Therefore, it is believed that the above liver tolerance dose could not be applied to cirrhotic liver, and it should be reduced, but it is not known exactly to reduce it to what extent. Table 5 showed that the mean dose to normal liver (MDTNL) was higher in patients with RILD compared to those without it by conventional RT fractionation (1.8–2 Gy per fraction). MDTNL was less than 30 Gy in HCC patients, which demonstrated the poor RT tolerance for HCC patients.

From the modern RT treatment plan system the detailed dose distribution, especially inhomogeneous dose distribution in liver, could be obtained as dose volume histogram (DVH). More accurate liver tolerance dose could be withdrawn. Different from conventional fractionated RT, another term to define normal liver volume is used as "non-involved normal liver," or "nontarget normal liver" (NTNL), which is the amount of total liver volume minus GTV. Table 6 summarizes the proposed dose constraints by hypofractionated RT with large fraction size of around 5 Gy per fraction, but with different endpoints to evaluate the hepatic toxicity, including RILD (classic or nonclassic), frequency of occurrences of CTCAE grade 3–4, or decline of Child-Pugh score. One could define what dose constraint of liver tolerance by readers was. Liang (2006) analyzed 109 HCC patients with hepatitis-induced hepatic cirrhosis, who were irradiated by 3D-CRT with median of 4–6 Gy per fraction. The liver tolerance dose (defined as no RILD) was mean dose

Table 5 Mean normal liver dose and radiation-induced liver disease in conventional fractionated radiation therapy

Study group	Patient number	Diagnosis	Baseline Child-Pugh class	Prescribed dose per fractionation to tumor	Crude percentage of RILD	Mean normal liver dose[a] in patients with vs. without RILD
Michigan (1995, 2002)	203	PLC + MLC	CP-A 203	1.5 Gy bid	9.4% (19/203)	37 Gy vs. 31.3 Gy
Cheng (2002)	68	HCC	CP-A 53 CP-B 15	1.8–2 Gy, qd	17.6% (12/68)	25.04 Gy vs. 19.65 Gy
Kim (2007)	105	HCC	CP-A 85 CP-B 20	2Gy, qd	12.3% (13/105)	25.4 Gy vs. 19.1 Gy

PLC primary liver cancer, *MLC* metastatic liver cancer, *HCC* hepatocellular carcinoma, *CP-A/B* Child-Pugh class A/B, *bid* twice fractions a day, *qd* one fraction a day, *RILD* radiation-induced liver disease

[a]Normal liver volume: liver volume minus gross tumor volume

Table 6 The proposed dose constraints of non-involved liver irradiated by hypofractionated irradiation

	Patient number	Tumor dose (Gy)/ fraction number	Endpoint of hepatic toxicity	Dose constraint	References
Child-Pugh A					
Mean dose	101 93	36 (24–54)/6 53.6 ± 6.6/11	C-P score ≥2[a] RILD	<20 Gy <23 Gy	Velec (2017) Liang (2006)
DVH	93		RILD	V5 < 86%, V10 < 68% V15 < 59%, V20 < 49% V25 < 35%, V30 < 28% V35 < 25%, V40 < 20%	Liang (2006)
	42	55 (30–60)/5(3–6)	C-P score decline	V25 < 32%	Dyk (2015)
	85	39–50/3–5	RIHT ≥ 1[b] RIHT ≥ 2[b]	V15 ≤ 21.5% V15 ≤ 33.1%	Su (2018)
Child-Pugh B					
Mean dose	21 16	40/5 53.6 ± 6.6/11	RIHT G3–4[c] RILD	≤8.82 Gy <6 Gy	Lasley (2015) Xu (2006)
DVH	21	40/5	RIHT G3–4	V7.37 < 33% V < 2.5 Gy = 810.8 cc V < 5 Gy = 1024.1 cc V < 7.5 Gy = 1149.7 cc V < 10 Gy = 1293.0 cc V < 12.5 Gy = 1432.0 cc V < 15 Gy = 1515.9 cc	Lasley (2015)

DVH dose volume histogram, *C-P score* Child-Pugh score, *RIDL* radiation-induced liver disease
[a]Child-Pugh score dropped ≥2
[b]Radiation-induced hepatic toxicity C-P score dropped ≥1, or ≥2
[c]Radiation-induced hepatic toxicity G3-4 (CTCAE)

to non-involved liver of 23 Gy. From the analysis of dose volume histogram (DVH), a tolerable DVH curve was regressively drawn for HCC with Child-Pugh A (Fig. 1).

QUANTEC recommended a liver dose constraint (Table 7). However, this dose constraints should be used with cautions as the different underlying liver, and the inhomogeneous dose distribution would make the dose constraint uncertain. For SBRT/SARB the recommended constraint is just for RT plan with fraction number from 3 to 6.

In summary, for conventional fractionated RT the liver tolerance is known, but is not totally known for hepatic background with different degrees of hepatic injury. For hypofractionated RT, what is the liver tolerance as the dose constraints for treatment planning needs further investigation in clinical practice, with special attentions to the factors, which influence RT tolerance, including the severity of hepatic cirrhosis, inhomogeneity of dose distribution, and fraction size.

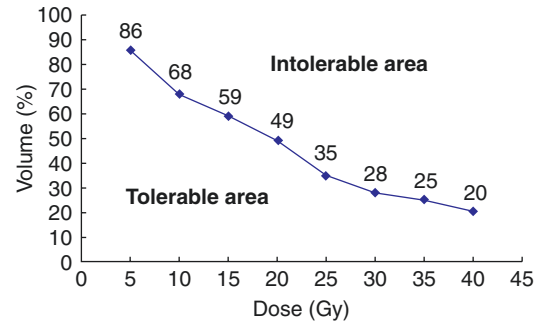

Fig. 1 A tolerable dose volume histogram (DVH) for primary liver cancers irradiated by hypofractionated irradiation

3.4 RT Method

Currently 3D-CRT, IMRT, RapiArc (RA), and helical tomotherapy (Tomo) are commonly used in clinic to treat HCC. However, the advantages and disadvantages and the appropriate indications for those RT techniques are under investigation.

Table 7 Quantitative analysis of normal tissue effects in the clinic (QUANTEC) recommendations for dose constraints during external beam radiation therapy (RT) to the liver

	Liver metastases	Primary liver cancer	Comment
Whole-liver RT	≤30 Gy, 2 Gy/fx 21 Gy/7 fx	≤28 Gy, 2 Gy/fx 21 Gy/7 fx	Whole-organ prescription dose
Partial-liver RT, conventional fractionation	≤32 Gy	≤28 Gy	Mean normal liver[a] dose for tumor dose ≤2 Gy/fx
SBRT, 3–6 fx	<15 Gy/3 fx <20 Gy/6 fx	<13 Gy/3 fx <18 Gy/6 fx CP B:<6 Gy/4–6 fx	Mean normal liver[a] dose
	At least 700 cc normal liver <15 Gy/3 fx At least 800 cc normal liver <18 Gy/3 fx		Critical volume model Only for Child-Pugh class A

SBRT stereotactic body radiation therapy, *fx* fraction, *GTV* gross tumor volume, *CP* Child-Pugh class
[a]Normal liver: the total volume of liver minus the gross tumor volume

Gong did a dosimetric study to compare 3D-CRT, IMRT, and RA at the end inspiration hold (EIH), end expiration hold (EEH), and free breathing (FB) techniques. RA resulted in better conformity index and homogeneity index than IMRT and 3D-CRT for the three breathing techniques ($p < 0.05$). The RA and IMRT significantly reduced the mean dose, V20, V30, and V40 of normal liver compared to 3D-CRT, while the V5 and V10 in RA were higher than in IMRT. In addition, the treatment time by RA was equal to 3D-CRT, which was significantly shorter than IMRT (Cheng et al. 2002).

Jin compared Tomo to fixed-beam IMRT plan in a dosimetric study. It was found that Tomo was better than fixed-beam IMRT in homogeneity index (1.35 vs. 1.27, $p < 0.001$) and conformity index (1.24 vs. 1.30, $p = 0.008$), but the mean NTNL-V15Gy (NTNL-V15) decreased remarkably in the fixed-beam IMRT plan (34.8%) compared to 41.1% in Tomo plan ($p < 0.001$). The mean total liver dose was also lower in the fixed-beam IMRT plan than Tomo plan (13.3 Gy vs. 15.6 Gy) ($p < 0.001$). The probability of RILD was estimated based on mean NTNL-V15Gy. The mean NTNL-15Gy were 41.1% and 34.8% for Tomo and fixed-beam plan, and the correspondent probabilities of RILD were 0.216 and 0.115, respectively (Song et al. 2015).

Hsieh in a dosimetric study showed that Tomo was better in uniformity than coplanar IMRT, and less normal liver V30Gy (21% in IMRT vs. 17% in Tomo). However, the V10Gy was higher with Tomo than IMRT (72.5% in Tomo vs. 64.8% in IMRT) (Hsieh et al. 2010).

Zhao (2016) recently published dose comparisons among 3D-CRT, IMRT, and Tomo. They found no significant differences between the mean dose to NTNL, liver V5 to V30, except for V20 between IMRT and Tomo. However, the above parameters in 3D-CRT were higher than IMRT and Tomo.

A retrospective study was done to compare 3D-CRT and image-guided IMRT for HCC by Yoon (Yoon 2014). 3D-CRT was used in 122 patients and IMRT 65 patients. IMRT delivered higher doses than 3D-CRT (mean BED 62.5 Gy vs. 53.1 Gy, $p < 0.001$). IMRT showed significantly higher 3-year OS (33.4% vs. 13.5%, $p < 0.001$), PFS (11.1% vs. 6.0%, $p = 0.004$), and IFFS (46.8% vs. 28.2%, $p = 0.007$) than 3D-CRT. In spite of retrospective study it really showed the advantage of IMR over 3D-CRT.

It was evident that 3D-CRT was inferior to IMRT, RA, and Tomo in terms of homogeneity and conformity, and dose to liver. RA and Tomo produced better dose homogeneity and conformity compared to IMRT, especially for intrahepatic multiple lesions, but at the expense of large volume of low dose to the normal liver. The advantage of fixed-beam IMRT is the decrease of low-dose volume of normal liver. Which method is better?

In liver cancer irradiation, especially for HCC, RILD is a fatal irradiation complication

and no medications or treatments are available. Therefore, prevention of RILD is paramount when liver irradiation is planned.

What are the risk factors to produce RILD? Besides liver cirrhosis, the dose to NTLD is critical. Mean dose to NTNL is most important. However, the parameters from DVH are also useful to predict RILD. Son (2013) found that the normal liver V15 was the most significant factor for RILD. Liang also reported that V20 was the most significant dosimetric parameter for the risk of RILD, and the cutoff value was 48.5%. It had suggested that the large volume effect of the liver was still important (Guha and Kavanagh 2011; Pan et al. 2010). Therefore, reducing the volume of low-dose region in NTNL is crucial to prevent RILD. Overall, RA and Tomo deliver a larger volume with a low dose than IMRT. Thus, use of IMRT could be the choice in HCC irradiation, especially when low-dose volume is big, like NTNL-V15 and –NTNL-V20. IMRT with the limited beams is likely to reduce low-dose volume.

The histopathologic feature of RILD is veno-occlusive disease (VOD), which results in classic RILD. In the nonclassic RILD, hepatocellular loss and dysfunction secondary to radiation-induced mitotic catastrophe of regenerating hepatocytes are the features. To prevent RILD, besides decreasing dose to NTNL it is very important that the normal liver should be protected from irradiation as much as possible and keep a part of normal liver not irradiated. It is well known that the liver has very strong capability to proliferate once it is damaged, like after surgery. Animal studies on rats have shown that normal liver could be stimulated to proliferation after partial irradiation; moreover, low-dose irradiated liver could also proliferate (Zhao et al. 2009; Ren et al. 2012). Further studies on rats with thioacetamide-induced cirrhosis liver showed the same phenomenon, and the nonirradiated and low-dose irradiated cirrhotic liver could repopulate, but the capability was worsened (Gu et al. 2011). Although the low-dose irradiated liver has the capability to proliferate, however, it is not known what is the dose threshold, after which the liver loses its proliferation capability. Therefore, it is wise to protect a part of liver totally avoiding irradiation so as to make this part of liver proliferating to compensate the loss of liver function after irradiation injury. Considering the issue of liver proliferation, it is preferable to use fixed-beam IMRT to treat HCC, instead of RA and Tomo, as the entire liver is explored to irradiation in RT and Tomo. However, this proposal needs to be confirmed by clinical practice.

In recent years, particle RT, proton, and carbon ion RT have been used for liver cancer more frequently than before. To compare the dose distributions by photon, proton, and carbon ion a dosimetric comparison study was done in eight HCC patients treated in Shanghai Proton and Heavy Ion Center (Wang n.d.). It showed that proton and carbon ion RT delivered much less doses to NTNL, right kidney, and stomach than X-ray, when tumor dose of 60 GyE was delivered with similar dose coverage (Fig. 2 and Table 8). Comparing carbon ion to proton, carbon ion gave less dose to kidney, but more dose to stomach (Table 8). For carbon ion, besides less dose to nontarget liver than proton, it has more advantage over proton for liver tumor location adjacent to gastrointestinal tract. Figure 3 shows that carbon ion delivers less doses to duodenum and colon (Wang et al. 2018). The reason for the less dose to gastrointestinal tract is the sharp penumbra of carbon ion, which is smaller than proton. Therefore, when the gastrointestinal tract locates laterally to the axis of beam direction, carbon ion hits it less. From the dosimetric comparison carbon ion has more dosimetric advantages than proton in less doses to nontarget liver and gastrointestinal track.

Although the patient number treated by proton and carbon ion RT was much less than by photon the outcome has shown better local control and survival, and less hepatic toxicity. However, due to unavailability of the facilities and the expensive cost their application has been limited. Moreover, their optimal dose and fractionation have not been concluded yet.

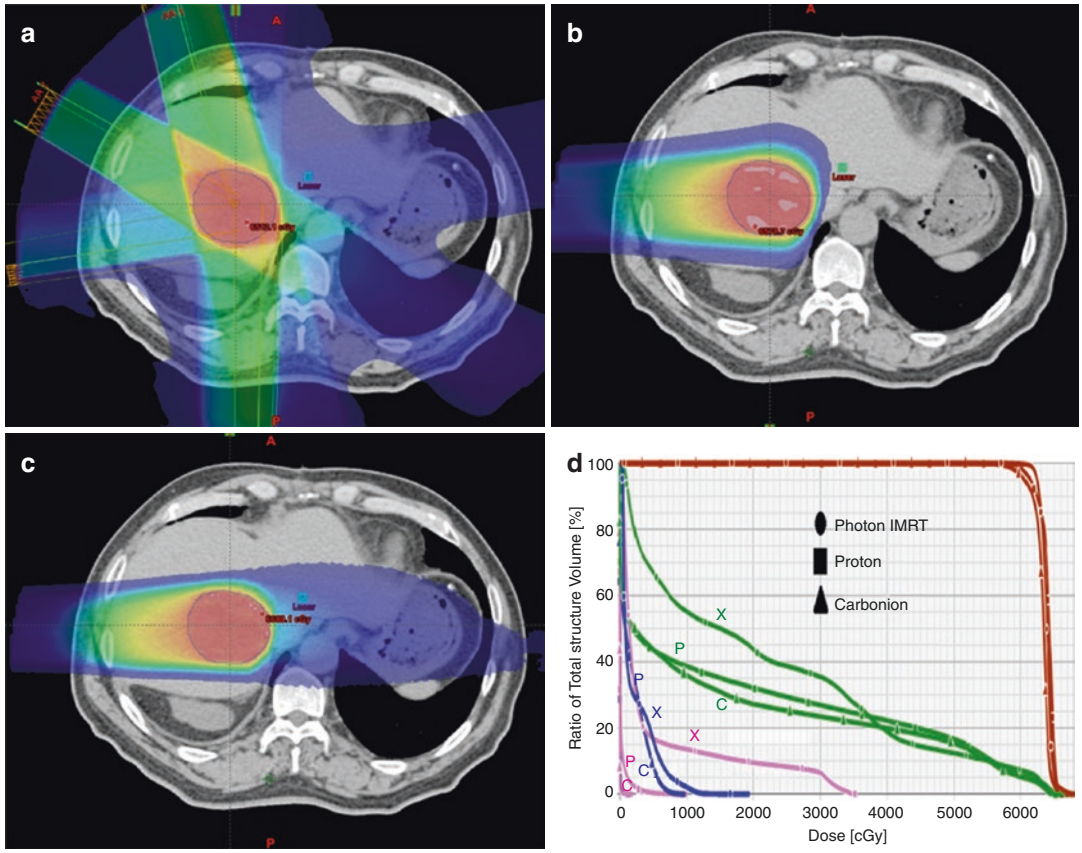

Fig. 2 Dose distribution comparison in one hepatocellular carcinoma patient. (**a**) Photon IMRT: 6 Gy/fraction for 10 fractions; (**b**) intensity-modulated proton irradiation: 6 GyE/fx for 10 fractions; (**c**) intensity-modulated carbon ion irradiation: 6 GyE/fx for 10 fractions; (**d**) dose-volume histograms for target (brown), nontarget liver (light green), kidney (pink), and stomach (blue) irradiated by photon (X), proton, and carbon ion, respectively

Table 8 Comparison of doses to liver, right kidney, and stomach using intensity-modulated irradiation (IMRT), intensity-modulated proton radiation therapy (IMPT), and intensity-modulated carbon ion radiation therapy (IMCT) for 8 hepatocellular carcinoma patients treated in Shanghai Proton and Heavy Ion Center

Dose parameter	Photon (X)	Proton	Carbon ion
ITV coverage (V95%)	99.8 ± 3.2	99.6 ± 4.8	99.9 ± 3.7
Nontarget liver			
Mean dose (GyE)	23.17 ± 4.30*	17.00 ± 2.92$^{\#}$	15.49 ± 2.62$^{\$}$
Kidney			
Mean dose (GyE)	5.91 ± 10.7^{+}	2.84 ± 8.46$^{\&}$	2.00 ± 9.41$^{=}$
Stomach			
Max dose (GyE)	29.92 ± 7.10**	2.61 ± 13.55$^{\#\#}$	10.03 ± 12.79$^{\$\$}$

All figures shown are mean ± sd

t-test: * vs. #, $p = 0.00$; * vs. $, $p = 0.00$; # vs. $, $p = 0.01$

+ vs. &, $p = 0.02$; + vs. =, $p = 0.01$; ** vs. ##, $p = 0.00$; ** vs. $$, $p = 0.00$; ##, vs. $$, $p = 0.01$. For all other comparisons between 2 parameters p were >0.05

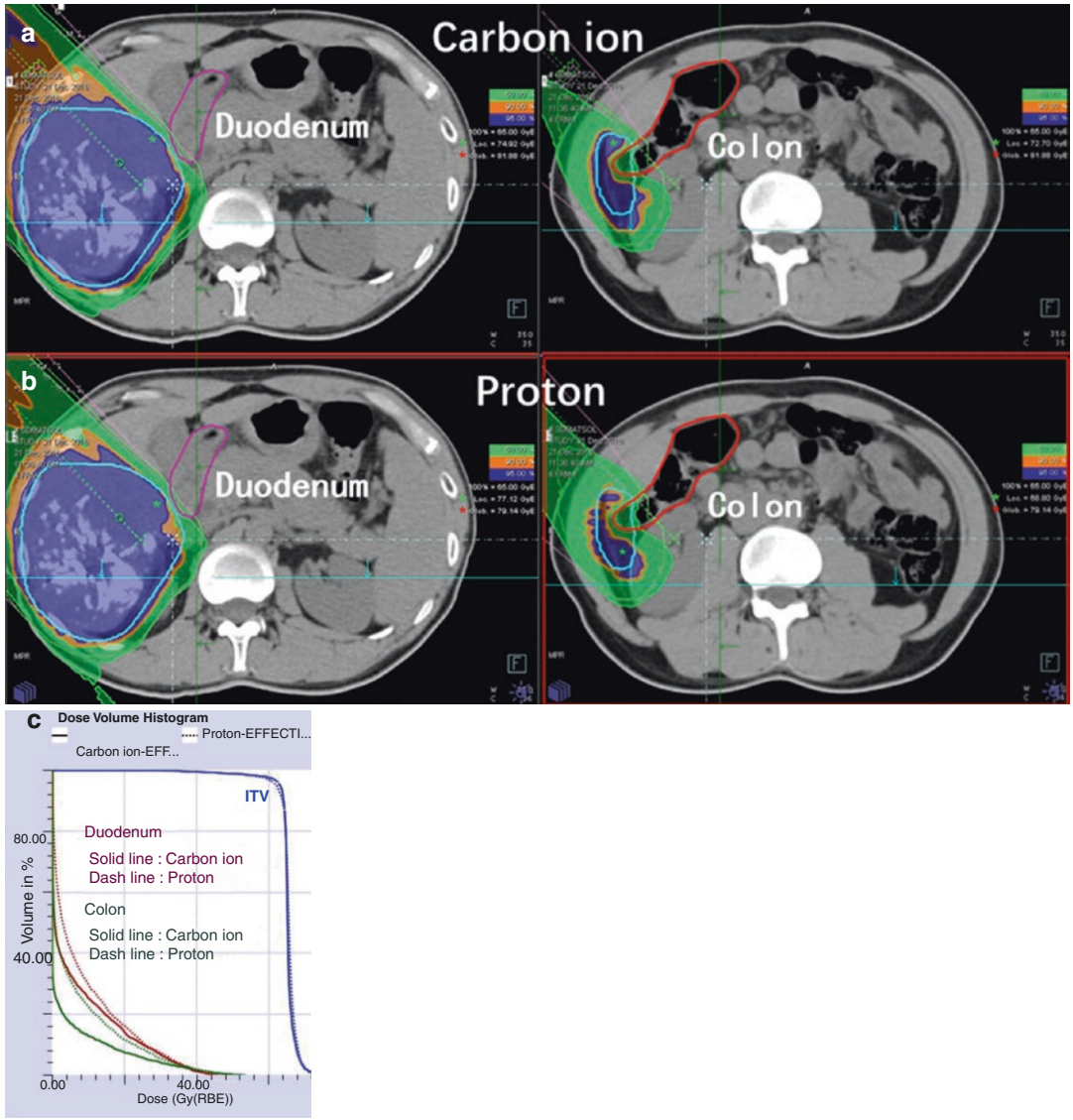

Fig. 3 Dose distributions of intensity-modulated proton and intensity-modulated carbon ion irradiation for liver cancer located adjacent to gastrointestinal tract. (**a**) Carbon ion; (**b**) proton; (**c**) dose volume histogram

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