Review Article

Pathologic response after modern radiotherapy for non-small cell lung cancer

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Abstract: In non-small cell lung cancer (NSCLC), pathologic complete response (pCR) following radiotherapy treatment has been shown to be an independent prognostic factor for long-term survival, progression-free survival and locoregional control. PCR is considered a surrogate to therapeutic efficacy, years before survival data are available, and therefore can be used to guide treatment plans and additional therapeutic interventions post-surgical resection. Given the extensive fibrotic changes induced by radiotherapy in the lung, radiological assessment of response can potentially misrepresent pathologic response. The optimal timing for assessment of pathologic response after conventionally fractionated radiotherapy and stereotactic ablative radiotherapy (SABR) remains poorly understood. In this review, we summarize recent literature on pathologic response after radiotherapy for early stage and locally advanced NSCLC, we discuss current controversies around radiobiological considerations, and we present upcoming trials that will provide insight into current knowledge gaps.

Keywords: Stereotactic ablative radiotherapy (SABR); non-small cell lung cancer (NSCLC); pathologic complete response (pCR)

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Introduction

In non-small cell lung cancer (NSCLC), pathologic complete response (pCR) following neoadjuvant chemoradiotherapy (CRT) has been shown to be an independent prognostic factor for progression-free survival, overall survival (OS) and locoregional control (1). In addition to providing insight as to treatment efficacy, accurately recognizing complete response in both early stage and locally advanced NSCLC (LA-NSCLC) is important for defining patient prognosis, determining the need for further adjuvant therapy, and guiding optimal follow-up evaluation (2). However, pathologic response after lung radiotherapy has been reported in only a small number of trials, most frequently in the setting of a historical interest for neoadjuvant irradiation in locally advanced lung cancer. In the context of stereotactic ablative radiotherapy (SABR) in early stage NSCLC, given that the majority of patients offered this treatment are not surgical candidates, the literature on pathologic response has, until recently, been inexistent. In addition, the disparity in pCR definitions across trials further complicates the interpretation of outcomes. In fact, there is a range of definitions of pCR, varying between the absence of viable tumor cells within a surgically-resected specimen to the presence of complete fibrosis or necrosis, as assessed by conventional histology

upon light microscopy (3). Hellmann *et al.* proposed the use of the term "major pathologic response", defined as 10% or less residual viable tumour, as another surrogate endpoint given its association with OS (3). Pataer and colleagues observed that among patients with NSCLC treated with neoadjuvant chemotherapy, each additional percentage of viable tumor post treatment was associated with a 1% increase in the risk of death (4). The Swiss Group for Clinical Cancer Research had defined pCR as "necrosis more than or equal to 95% and fibrosis on pathologic examination" (5).

In the current review, we will discuss the results from the recent MISSILE-NSCLC ("Measuring the Integration of Stereotactic Radiotherapy Plus Surgery in Early Non-Small Cell Lung Cancer") phase II trial on pathologic response after neoadjuvant SABR in early-stage NSCLC (6) as well as the major studies reporting pathologic response after conventionally fractionated radiotherapy +/– systemic therapy in LA-NSCLC. Current controversies on the optimal timing and methods for assessment of pathologic response, considering radiobiological mechanisms, will be discussed. Finally, on-going trials of combined radiotherapy and immunotherapy in the neoadjuvant setting will be reviewed.

The case of early stage NSCLC

Challenges of radiological assessment of response after SABR

SABR is effectively the gold standard treatment approach in patients with inoperable stage I NSCLC, with local control rates as high as 90% at 5 years (7-14). The role of SABR in operable or marginally operable patients is currently being assessed in the context of several on-going randomized controlled trials (NCT02984761, NCT02629458, NCT01753414, NCT02468024).

One of the main challenges in monitoring outcomes after SABR in inoperable patients is distinguishing radiological peri-tumoral fibrotic changes from tumor recurrence (6,15,16). As such, 50% of patients treated with SABR will show signs of radiological progression on computed tomography (CT) imaging following SABR (17), while 90% will develop late fibrotic changes (18-20) at a median time of 4 months and frequently after 1 year (18-20), making radiological evaluation of response unreliable. Therefore, the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, which rely strictly on tumor dimension changes, are not optimal for response assessment post-SABR (21). To address this gap, retrospective studies and systemic reviews have identified radiologic predictors of disease persistence and/or progression, which include a combination of morphological findings on serial CT along with post-SABR maximum standardized uptake value (SUV_{max}) ≥5.0 on 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) (16,22-24). While no definitive guidelines exist, the use of these predictors has been widely adopted in the clinical setting as it is considered the best available strategy to distinguish post-SABR parenchymal changes from disease persistence and/or progression (25). In this radiological approach, persistent enlargements on CT may not count as local failure, which may lead to overestimation of local control rates. In addition, concurrent benign inflammatory glucose uptake that can occur up to 12 months post-SABR complicates 18-FDG-PET interpretation (15). In view of these limitations, pathologic assessment of response after SABR remains the gold standard to evaluate the absence of viable tumor cells. In the context of the growing role of SABR, better understanding of the histological changes underlying the radiological observations, for clearer insight into treatment efficacy, is essential for optimization of subsequent therapies and follow-up.

Evidence for pathologic response post SABR

In the hopes of increasing treatment potency, decreasing positive margin rates, and gaining understanding of the expected pathologic responses, the group from London Health Sciences Centre undertook a phase 2 clinical trial aiming at examining pCR rate after neoadjuvant SABR in operable early stage NSCLC patients (*Table 1*) (6). The MISSILE-NSCLC trial enrolled 40 operable patients with histologically confirmed clinical T1-T2aN0 NSCLC treated with standard dose lung SABR (54–60 Gy in 3–8 fractions, corresponding to biologically effective dose >100 Gy_{10}), followed by surgery (lobectomy or sublobar resection) at a median time of 10 weeks (range, 9–16 weeks) post-SABR completion (6). A lobectomy or sublobar resection was performed in 90% of patients, along with sampling of hilar and mediastinal lymph nodes; 10% of patients did not undergo surgery due to radiation-induced pneumonitis, poor performance status, pulmonary function precluding operability, or regional disease progression (6).

Tumor cell viability was assessed by standard

Table 1 Pathologic complete response rates after neoadjuvant SABR for resectable early-stage NSCLC

Author	Trial name	Year	Treatment regimen	N surgically-resected*	pCR rate	Time between neoadjuvant therapy and resection	Comment
Palma *et al*.	MISSILE-NSCLC (NCT02136355)	2019	Neoadjuvant SABR plus surgery	35	60%	10 weeks	2-year OS: 77% 2-year local control: 100% 2-year regional control: 53% 2-year distant control: 76%

*, one pathology specimen was improperly fixated in formalin and thus could not be analyzed. SABR, stereotactic ablative radiotherapy; N, number of patients; NSCLC, non-small cell lung cancer; pCR, pathologic complete response.

hematoxylin-eosin staining and morphologic appearance of tumor cells on microscopy. While a pCR rate of 90% was hypothesized based on historical local control outcomes of lung SABR, the investigators reported a pCR rate of only 60% at 10 weeks post-SABR. At 8 weeks post-SABR, he corresponding complete and partial radiological responses were 2% (1 patient) and 43% (17 patients), respectively. In surgically operated patients, 2-year OS, local control, regional control and distant control was 77%, 100%, 53% and 76%, respectively. While the reported pCR may seem strikingly inconsistent with the high clinical local control observed in previous studies, there are multiple possible underlying explanations. The kinetics of post-SABR pathologic response are largely unknown, and many have hypothesized that the ultimate pCR rate could be underestimated at 10 weeks (26). This is consistent with current radiobiological models supporting that in addition to apoptosis, post-mitotic death is a major mechanism of cellular death after radiotherapy. In this model, unrepaired DNA damage leads to cell inactivation during mitosis, with a critical level of genomic instability reached sometimes only after several cycles of cell division (27-30). In this context, tumor cells can appear viable on histopathology but in fact are dead, dying, or senescent from lethal chromosomal damage. With the caveat of different treatment techniques and modality combination, this is analogous to previous evidence in anal canal cancer treated with CRT, where the optimal time for assessment of response was found to be at 26 weeks post-treatment, as many patients with partial response at 11 weeks finally developed complete response by 26 weeks (31). Increased pCR rates with increasing time from radiotherapy completion have also been reported in rectal and esophageal cancers (32-34). However, it is unclear if these findings can be directly translated to SABR, where the radiobiological effect is thought to also involve vascular damage and deterioration of the intratumor environment leading to tumor cell death (35). It is however possible that early assessment of pathologic response at 10 weeks post-SABR is poorly representative of the actual radiotherapy damage and clonogenic survival.

On the other hand, an alternative explanation is that pCR is indeed lower than expected after lung SABR. In fact, in a subgroup analysis by median time from the end of SABR to surgery (<74 *vs.* ≥74 days), pCR remained 60% in both groups. The high local control rates of SABR reported in the literature are derived from largely inoperable patients population with multiple comorbidities, and one may argue that these rates are subject to competing risk of death from other causes. In addition, as previously stated, radiological assessments of local control with current methods may underestimate disease persistence due to the confounding fibrotic changes. In a recent orthotopic model of NSCLC in rats, Oweida *et al.* induced NSCLC in 11 rats, of which 5 were assigned to observation and 6 received a SABR dose of 34 Gy in one fraction (36). Animals were sacrificed at different time points (10, 30 and 60 days post-SABR) to evaluate radiologic and histologic responses to SABR longitudinally. Radiologically, 4/6 animals had CR with disappearance of tumor on imaging within 30 days of therapy, 1 had partial response and 1 had radiologic progression. Interestingly, radiologic responses were found to match the observed pathologic responses: the 4 animals with CR had radiation-induced pneumonitis upon histology, and moderately differentiated mucinous adenocarcinoma was present in the two tumors that showed either partial response or progression (36).

Current SABR literature as well as our current knowledge of radiobiological effects of radiotherapy suggest

that the outcomes from MISSILE likely underestimate the actual pCR after SABR and should be considered with caution. However, MISSILE certainly highlights the critical need for better understanding of the pathological efficacy of SABR and reiterates that SABR alone should be used with vigilance in operable patients outside of the on-going clinical trials.

The case of locally advanced NSCLC

The current standard treatment in patients with LA-NSCLC (stage IIIA/IIIB) is concurrent CRT followed by adjuvant durvalumab based on the recently published PACIFIC trial (37). In comparison to SABR, pathologic response is more extensively reported in LA-NSCLC given the multiple previous trials that studied neoadjuvant approaches in this patient's population with the aim of improving the historically dismal outcomes. These past studies typically included highly heterogenous groups of patients and generally showed no survival advantage to the addition of surgery to CRT. However, selected patients may have improved outcomes from neoadjuvant treatments and, in the era of immunotherapy, this approach is now being revisited in on-going clinical trials.

Pathologic response after neoadjuvant radiotherapy in locally advanced NSCLC

Data on pathologic response after conventional radiotherapy alone in LA-NSCLC is provided by the historical use of neoadjuvant radiotherapy followed by surgical resection (38-43) (*Table 2*). The Lung Cancer Study Group (LCSG 881) compared preoperative radiotherapy (44 Gy in 22 fractions) and preoperative chemotherapy (mitomycin, vinblastine and cisplatin) in a total of 67 stage III patients. The median survival was 12 months in both arms, and only 1 patient developed pCR in each arm (41). The randomized control trial from the Cancer and Leukemia Group B (CALGB 9134) compared neoadjuvant chemotherapy (cisplatin and etoposide) to standard fractionation neoadjuvant radiotherapy (40 Gy in 20 fractions) and was closed prematurely due to slow patient accrual. No difference was found between nodal downstaging, survival or rates of complete surgical resection, and pCR in the radiation arm was 0% (40,43). Given the increased toxicity of neoadjuvant radiotherapy alone, along with the failure to improve survival outcomes, these studies led to the abandonment of this approach.

Pathologic response after neoadjuvant chemoradiation in locally advanced NSCLC

The demonstration of a modestly improved OS with the combination of CRT in inoperable patients (44,45) led to a subsequent interest in trimodality therapy with the aim of improving the persistently dismal prognosis of these patients. Several studies of preoperative cisplatin-based chemotherapy and radiotherapy have evaluated the pathologic response in LA-NSCLC and have demonstrated pCR rates varying from 17% to 45% (*Table 3*) (46-53). The most important studies are summarized below.

The phase III randomized control trial of the North American Intergroup trial 0139 (INT0139) compared neoadjuvant CRT (cisplatin, etoposide, plus 45 Gy) followed by surgery 3–5 weeks later *vs.* definitive CRT in patients with T1-3N2M0 NSCLC (51). PCR was achieved in 18% of 164 patients that underwent a thoracotomy following neoadjuvant CRT (51). The Southwest Oncology Group 9416 trial/North American Intergroup 0160 trial reported 34% pCR at 3–5 weeks after neoadjuvant CRT consisting in a combination of cisplatin and etoposide delivered concurrently with fractionated radiotherapy to a dose of 45 Gy (46,47). Importantly, the latter trial showed that pCR was associated with improved OS. In fact, at a median follow-up of 84 months, median survival was 30 months in patients with minimal microscopic disease and 29 months in patients with gross residual disease, while it was not reached in patients with pCR (46,47) The subsequent Japanese Clinical Oncology Group 9806 study used concurrent mitomycin, vindesine, cisplatin and radiotherapy to dose of 45 Gy in superior sulcus tumors, followed by surgical resection at 2–4 weeks and reported 6-year OS of 56% and pCR of 21% (12/57 patients) (48). The Radiation Therapy Oncology group 0229 study attempted curative radiation doses reaching 61 Gy, in combination with carboplatin and paclitaxel, followed by surgery within 8 weeks of CRT completion, but pCR was only 8%, casting doubts on the potential of conventionally fractionated dose escalation to improve pCR rates (54).

While the above-mentioned studies reported outcomes of standard fractionation radiotherapy, additional studies looked at the role of hyperfractionated radiotherapy combined with chemotherapy to further improve outcomes. Two landmark phase III trials conducted in LA-NSCLC (55,56) suggest that radiation dose escalation through accelerated-hyperfractionation could be a promising

Table 2 Pathologic complete response rates after neoadjuvant radiotherapy

Study	Group/Trial name	Study type	Year	Treatment regimen	N surgically-resected	pCR rate	Time between neoadjuvant therapy and resection	Comment
Wagner *et al.*	LCSG 881	Phase II trial	1994	Neoadjuvant RT (44 Gy in 22 fx)	12	8%	8 weeks	Median survival: 12 months
Elias *et al.*	CALGB 9134	Phase II trial	2002	Neoadjuvant RT (40 Gy in 20 fx)	24	0	2–3 weeks	Closed prematurely. No difference between nodal downstaging, DFS and OS and rates of complete surgical resection between neoadjuvant RT *vs.* CT

pCR, pathologic complete response; CT, chemotherapy; RT, radiotherapy; OS, overall survival; DFS, disease-free survival; Fx, fraction; N, number of patients.

approach to increase pCR rates. The ESPATUE trial evaluated induction chemotherapy (cisplatin and paclitaxel) with concurrent CRT (45 Gy, 1.5 Gy twice daily) in stage IIIA-B NSCLC and showed pCR in 33% of 81 resected specimens (55). The German Lung Cancer Cooperative Group phase III trial approach consisted of three cycles of cisplatin and etoposide, followed by accelerated-hyperfractionated radiotherapy (45 Gy, 1.5 Gy twice daily) with concurrent carboplatin and vindesine (56). Interestingly, the latter study did not define pCR rates as complete absence of viable tumor cells, but rather defined histopathological response as less than 10% of residual tumor cells on hematoxylin and eosin stain. At 4–6 weeks post CRT, 60% of 98 patients had a histopathological response with less than 10% residual tumor cells (56).

Predicting pCR

PCR analysis may help determine early signs of therapeutic efficacy, years before survival data is available and could determine the necessity for additional adjuvant therapeutic interventions (2). There must be a balance between assessing pCR at an optimal timepoint to ensure it is a representative measure of therapy-induced cell damage, yet without compromising surgical resection and oncologic outcomes (57). From a radiobiological standpoint, we previously discussed that later pCR assessments are more likely to grasp the effect of mitotic death induced by radiotherapy. However, the clinical literature in LA-NSCLC suggests that prolonged time before surgical resection after completion of neoadjuvant therapy may jeopardize cancer outcomes. In fact, a large retrospective study from the National Cancer Database of 1,623 patients with stage IIIA NSCLC found significantly improved survival in patients operated at 0–3 weeks post-CRT (30%), compared to those operated at 6–9 weeks (20%, P=0.04) (58). In patients with LA-NSCLC selected for trimodality approach, it is therefore common practice to aim for rapid restaging and resection within 6 weeks from neoadjuvant therapy completion. This being said, it should be restated that the survival advantage of the addition of surgery to concurrent CRT has not been shown, and that the recent results from the PACIFIC trial have established radical CRT and adjuvant immunotherapy as a standard of care in LA-NSCLC. Nonetheless, predicting pCR in LA-NSCLC treated with CRT could be critical for optimal selection of patients who may benefit from additional treatment intensification (52).

Current literature suggests that symptom improvement (brachial plexus-related) in superior sulcus tumors, pre-operative radiation dose over 54 Gy and the percent reduction in tumor size post CRT are associated with pCR (52,53). Haque *et al.* retrospectively analysed 1,750 patients from the National Cancer Database from 2004–2015 that underwent neoadjuvant CRT for histologically confirmed T1-4N2M0 NSCLC. This study confirmed the improved prognosis of patients who achieved pCR (median OS in pCR =72 months *vs.* others =40 months) (53). Though radiation dose over 54 Gy was associated with pCR, doses above 59.4 Gy resulted in higher postoperative mortality, suggesting that increasing radiation dose to augment radiation efficacy may be more toxic and requires careful investigation. Antonoff *et al.* (52) focused on superior sulcus tumors and found, on univariate analysis, that symptom improvement (abatement of pain or neurological symptoms secondary to compression of the brachial plexus) and tumor size reduction on CT were associated with pCR, but not radiation dose. On multivariate analysis, only tumor size reduction on pre-operative imaging remained an independent predictor of pCR (52). PCR rate among patients with combined reduction in tumor size and improvement in symptoms was as high as 88%.

While robust predictors of pCR are still lacking, advances in the fields of functional imaging, radiomics and liquid-based genomics may aid in the non-invasive assessment of tumor response and prediction of cancer outcomes. In addition to simple anatomic assessments of tumor size, functional imaging can characterize tumor activity by measuring glucose uptake, perfusion, hypoxia and proliferation, all potential indicators of tumor cell viability (59). Furthermore, the emergence of minimally invasive "omic" approaches including radiomics (consisting in the extraction and analysis of quantitative features from radiologic images) (60-62) and liquid-based genomics (circulating tumor DNA and circulating tumor cells) (63), begin to show promise for response assessment in lung cancer; however, their investigation remains embryonic.

The disruptive advent of immunotherapy

Immune checkpoint blockade has recently completely changed the treatment paradigm in locally advanced and metastatic NSCLC, becoming standard of care as first line therapy in both settings (64,65). In fact, patients with metastatic NSCLC and without EGFR/ALK genomic aberrations are now offered pembrolizumab as first line therapy after demonstration of improved survival compared to platinum-based chemotherapy (66,67). More recently, results from the PACIFIC trial have disrupted the treatment paradigm in LA-NSCLC after showing significantly improved survival at 2 years in patients treated with adjuvant durvalumab after standard CRT (37). Although the increased potency of this new treatment combination suggests that pCR rates could be higher with the use of immunotherapy, the patterns of response and progression after immunotherapy seem to differ from those observed with conventional therapies, complicating both radiological and pathological assessments (68). A response tool better adapted to immunotherapy was developed in 2017, the immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) (69), but radiological assessments after immunotherapy remain challenging, even with the aid of these guidelines (70-72).

Forde *et al.* conducted the first pilot study of neoadjuvant programmed cell death 1 blockade in resectable lung cancer with nivolumab administered 4 weeks prior to surgery (73). Of 21 patients with stage I-IIIB NSCLC, 45% had a "major pathologic response" (less than 10% viable tumor cells on hematoxylin and eosin staining), and 14% had complete pathologic response as defined by the absence of viable tumor cells (73). It is postulated that radiotherapy could work synergistically with immunotherapy by modifying the immunosuppressive tumor microenvironment and strengthening the immunogenicity of tumor cells by increasing tumor neoantigens, activating dendritic cells and increasing T-cell recruitment (74-77). The advent of immunotherapy has renewed the interest for neoadjuvant therapy followed by surgical resection, as demonstrated by the several on-going trials evaluating the combination of neoadjuvant immune checkpoint inhibitors and radiotherapy +/– chemotherapy in resectable LA-NSCLC patients (NCT03237377, NCT02987998, NCT03871153) (74). The interest for immunotherapy has also been extended to SABR, where current efforts are centered on lowering regional and distant recurrence rates. As such, the combination of radiotherapy and immunotherapy is currently being evaluated in several trials delivering concurrent and adjuvant immunotherapy with SABR (NCT03217071, NCT03446911, NCT03574220, NCT03833154). In short, our current knowledge and understanding of pCR after radiotherapy +/– chemotherapy is limited, but will likely be further complicated and perhaps rendered obsolete with the widespread use of immunotherapy in NSCLC.

Table 3 Pathologic complete response rates for neoadjuvant chemoradiotherapy in locally-advanced NSCLC

Author	Group/Trial name	Study type	Year published	Treatment regimen	N surgically-resected	pCR rate	Time between neoadjuvant therapy and resection	Comment
Rusch *et al.*	SWOG 9416 and North American Intergroup 0160	Phase II trial	2001, 2007	Neoadjuvant CRT (cisplatin and etoposide with 45 Gy)	83	34%	3–5 weeks	pCR was an independent prognostic factor
Kunitoh *et al.* & Tsuboi *et al.*	JCOG 9806	Phase II trial	2008, 2010	Neoadjuvant CRT (mitomycin, vindesine, cisplatin and 45 Gy)	57	21%	2–4 weeks	7-year OS of 56%. pCR was an independent prognostic factor. 7-year OS of patients with pCR: 92%
Albain *et al.*	INT 0139, Loyola University	Phase III trial	2009	Neoadjuvant CRT (cisplatin and etoposide with 45 Gy)	164	18%	3–5 weeks	
Antonoff *et al.*	MD Anderson Cancer Center	Retrospective review	2016	Neoadjuvant CRT (most commonly employed chemotherapy: cisplatin and etoposide. Median RT dose: 45.0 Gy (range, 21–70 Gy)	75	32%	NA	Symptom improvement (brachial plexus neuropathy) and reduction in tumor size were associated with pCR. pCR and age were independent predictors of OS
Haque *et al.*	NCDB database, Houston Methodist Hospital and Allegheny General Hospital	Retrospective review	2019	Neoadjuvant CRT (CT regimens NA, minimum RT dose: 45 Gy)	1,750	17%	NA	No OS benefit with higher neoadjuvant RT doses. pCR associated with improved OS
Eberhardt *et al.*	ESPATUE	Phase III trial	2015	Neoadjuvant CRT (cisplatin and paclitaxel with 45 Gy)	81	33%	20–61 days (median: 37 days)	5-year OS greater than 40%
Kappers *et al.*	Netherlands Cancer Institute	Retrospective review	2008	Neoadjuvant CRT (cisplatin with 66 Gy)	12	67%	4–6 weeks	2-year OS in patients with pCR: 75% 5-year OS in patients with pCR: 39%
Marra *et al.*	University of Essen	Phase II trial	2007	Neoadjuvant CRT (cisplatin + etoposide or cisplatin + paclitaxel, with 45 Gy)	29	45%	4–6 weeks	5-yr OS 63% if pCR, compared with 35% if partial response
Thomas *et al.*	GLCCG	Phase III trial	2008	Neoadjuvant cisplatin and etoposide, followed by accelerated-hyperfractionated RT (45 Gy, 1.5 Gy daily) with concurrent carboplatin and vindesine	98	NA	4–6 weeks	60% of operated patients showed a major histopathological response

*, this table encompasses the principal studies, but does omit trials with small number of patients and studies published before the year 2000. Studies are listed in the order they are presented throughout the text. NSCLC, non-small cell lung cancer; CT, chemotherapy; RT, radiotherapy; pCR, pathologic complete response; CRT, chemoradiation; OS, overall survival; N, number of patients; NA, not available.

Conclusions

Evaluating pathologic response rates after lung radiotherapy is highly informative regarding treatment efficacy and patients' prognostication in order to help select patients most in need for treatment intensification. However, assessment of pCR is challenging, given that its definition is not uniform across studies and that the best timing for histological assessment of pCR after both conventional radiotherapy +/– chemotherapy and SABR is unclear. Our current response assessment methods, based on radiological evaluations, are certainly not optimal, and further studies correlating radiological and pathological findings as well as exploring the role of predictive biomarkers hold the promise to provide more accurate non-invasive response assessment methods. Finally, our current knowledge of pCR after neoadjuvant treatment will likely be profoundly challenged in the upcoming years by the integration of immunotherapy in the treatment of NSCLC.

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Footnote

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