Introduction

According to statistics, there were 18.1 million new diagnoses and 9.6 million deaths of malignant tumors worldwide in 2018. The top five incidence are lung cancer, female breast cancer, prostate cancer, colorectal cancer, and gastric cancer. Meanwhile, the top five mortality rates are lung cancer, colorectal cancer, gastric cancer, liver cancer, and breast cancer (1). With the increase of tumor incidence and mortality, treatments for tumors are also constantly updating, from traditional treatment such as surgical resection, chemotherapy and radiotherapy, to individualized treatment, such as endocrine therapy, targeted therapy, immunotherapy, etc. As these treatments expanding in scope, the criteria for evaluating their effectiveness are updating. RECIST 1.1 is currently the most accepted standard for evaluating the efficacy of solid tumors (2). In evaluating the therapeutic effects of cancer, objective response rate (ORR) is an effective surrogate endpoint for overall survival.
(OS) defined by RECIST 1.1, and widely used in clinical treatment. Nonetheless, clinical studies conducted by Gadgeel et al. (3) and Aix et al. (4) have indicated that ORR may not be able to adequately access therapeutic effects, which is not always related to progress free survival (PFS) or OS consistent. ORR is not a continuous metric, partial response ranges from 30% to 99%, this range is very wide and there may be some inaccuracies. RECIST 1.1 based on the change of tumor shrinkage, tumor shrinkage as a predictor have some limitations. First, tumor shrinkage measurements are based on the sum of the longest diameters of measurable target lesions, but non-measurable lesions cannot be considered. The reduction in the target lesions does not always result in a diameter reduction, because the tumor tissue can be replaced by necrotic or fibrous tissue, and these morphological changes cannot be accurately identified by computed tomography. Second, tumor shrinkage may not always be symmetrical, which may affected the measure of target lesions. Third, tumors metabolic response reflects the viability of neoplastic cells and correlated with patient outcome, 18F-FDG-PET CT can detect early metabolic changes in tumor cell metabolism before any change in tumor size occurs (5). In addition, the functional status of organ, the symptoms and subjective feelings of patients are also important. So, many factors need to be considered in predicting the prognosis of patients.

DpR has been used in hematologic malignancies and is considered as a predictor of efficiency. In multiple myeloma, DpR relate with M protein in the blood and urine and plasma cells, DpR can be used as a predictor for prognosis of non-solid tumor (6). In solid tumors, Mansmann et al. firstly proposed DpR as a surrogate endpoint in metastatic colorectal cancer (mCRC), and defined DpR as the maximum rate of reduction from the initial tumor burden (7). In 2015, Heinemann et al. conducted a systematic analysis of DpR as a measure of efficacy in three experiments, they realized that DpR can be a potential surrogate endpoint for mCRC patient (8). After that, researchers were inspired to study DpR, DpR has been applied in several kinds of solid tumors, for example, mCRC, lung cancer, gastric cancer, metastatic breast cancer, metastatic melanoma and advanced pancreatic cancer. DpR is a valuable surrogate endpoint for mCRC patients received anti-EGFR antibody, but the predictive value of DpR in other solid tumors need further studies. This review will summarize the application value of DpR in common solid tumors, aim to provide references for future clinical therapy.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2547).

**Methods**

The titles and abstracts or the full articles in the PubMed, Cochrane and CNKI databases were searched using the following search terms in titles and abstracts: ‘depth of response’ OR ‘deepness of response’. No language restriction was applied to the literature search and the search was limited to studies in humans. Original articles from 1987 through June, 2020 that reported randomized controlled trials (RCTs) that involve depth of response or deepness of response and solid tumors were included in this study. Articles not fulfilling all these criteria were excluded.

**Application of DpR in colorectal cancer**

Colorectal cancer is one of the most common malignancies, its mortality rate is second only to that of lung cancer, approximately a quarter of patients have already undergone distant organ metastasis at the time of initial diagnosis and cannot be treated by surgery (9). The treatment for patients with mCRC mainly includes chemotherapy with or without molecular targeting biologics, which can lower the clinical stage and add the opportunity to surgery (10-12). PFS and OS for patients with mCRC have been improved because of the combination of chemotherapy and molecular targeting biologics in the first-line treatment, such as cetuximab, panizumab and bevacizumab (13-15). As the median OS of patients is prolonged, the design of clinical trials and the choice of treatment regime urgently need an early alternative endpoint for OS, which promotes the proposal and application of DpR. Many studies about mCRC confirmed the predictive value of DpR in mCRC.

**Application of DpR in the chemotherapy combined with EGFR inhibitors for mCRC**

Mansmann et al. first proposed the definition of DpR—the maximum percentage of reduction from the initial tumor burden in 2013 (7). Through their analysis of CRYSTAL (16) and OPUS (17) clinical trials, they found that the combination of cetuximab and chemotherapy can obtain higher DpR and longer post progression survival (PPS), and OS, which emphasized that DpR can be used
as a new efficacy evaluation for clinical trials. Similar explorations have been carried out, and four reports (18-21) showed that DpR can predict the prognosis of RAS wild type mCRC patients receiving first-line chemotherapy-based cetuximab. In 2016, Tsuji et al. analyzed 54 patients who received FOLFOX combined with Cetuximab in JACCRO CC-05 phase II clinical trial, median DpR was 56.3%. DpR was related to OS and PPS (OS: rs=0.314, P=0.027; PPS: rs=0.366, P=0.017) (19). Furthermore, Sunakawa et al. collected 92 patients in JACCRO CC-05 and JACCRO CC-06 Phase II clinical trials, they found a correlation between CEA levels and DpR (rs=0.44, P<0.0001), and both DpR and CEA levels are related to clinical results of cetuximab first-line therapy (18).

DpR also showed its predictive value in the mCRC patients who received second-line chemotherapy with cetuximab. Osumi et al. published a report about 42 mCRC patients who received second-line FOLFIRI-based cetuximab, results showed that patients with DpR >30% have longer OS and PFS (22), firstly proving that DpR can be used as a new indicator of the efficacy for second-line treatment of mCRC.

In addition to cetuximab, another EGFR antibody—Panitumumab can also improve the DpR of RAS wild-type mCRC patients. Taieb et al. (23) conducted an exploratory analysis on PRIME (24), PEAK (25), and PLANET (26) trials to assess the impact of DpR on survival outcomes in patients with RAS wild-type mCRC received panitumumab. These results all suggested that DpR is correlated with PFS and OS (Table 1).

**Application of DpR in the chemotherapy for colorectal cancer**

In order to evaluate whether DpR is universally applicable to chemotherapy alone for mCRC, Nozawa et al. (27) conducted a study that consisted of 156 mCRC patients who received first-line chemotherapy regimens, FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin), CapeOX (capecitabine and oxaliplatin), or FOLFIRI (5-fluorouracil, leucovorin, and irinotecan). The study divided patients into two groups according to DpR <45% and DpR ≥45%. It indicated that patients whose DpR ≥45% was correlated with longer PFS (median 16.4 vs. 8.1 months for DpR <45%, P=0.006) and OS (median 58.6 vs. 30.9 months for DpR <45%, P=0.041). Similar results were also obtained in Kim et al.’s (28) retrospective study of patients receiving chemotherapy alone. PFS, OS, and PPS of patients with DpR ≥60% were significantly improved.

**Application of DpR in the combination of chemotherapy and Bevacizumab for colorectal cancer**

The TRIBE phase III trial compared the efficacy of first-line FOLFOXIRI plus bevacizumab with FOLFIRI plus bevacizumab for unresectable mCRC patients, demonstrating that FOLFOXIRI plus bevacizumab arm had a higher DpR (43.4% vs. 37.8%, P=0.003), longer PFS (9.2 vs. 7.2 months, P=0.024), and longer OS (30.4 vs. 26.9 months, P=0.213) than the other group, which firstly certified that DpR is associated with PFS, PPS and OS in these patients receiving chemotherapy-based bevacizumab (29).

However, there are still some limitations of these studies. Most of these research results were retrospective analysis and had not considered some factors that would affect efficacy, for example, primary tumor location (30-32) and BRAF mutation status (33-35). The optimal cut-off value of DpR has no definite conclusion. Whether DpR can be used as a predictor of PFS and OS still needs to be confirmed by large-scale prospective studies.

**Application of DpR in lung cancer**

Lung cancer is the leading malignancy in morbidity and mortality. In recent years, researches on treatment with advanced lung cancer have become the main research direction of lung cancer. The emergence of targeted therapy and immunotherapy have improved the prognosis of advanced NSCLC. The prolongation of survival and the varies of tumor regression trend have promoting the exploration of new efficacy evaluation indicator. DpR has been applied to chemotherapy, targeted therapies and immunotherapy in patients with lung cancer. However, whether DpR can be used as an indicator for evaluating the efficacy of lung cancer is currently controversial.

**Application of DpR in chemotherapy of lung cancer**

Chemotherapy plays an important role in the treatment of tumor. Before the advent of immunotherapy, chemotherapy was the commendatory treatment for advanced NSCLC without known driver mutations. For NSCLC, CA031 trial (36) divided patients into four groups based on the degree of DpR (Q1: >0% to 25%, Q2: >25% to 50%,
Q3: >50% to 75%, Q4: >75%), and these 4 groups were compared with a group in which patients who had no tumor shrinkage or tumor enlargement. Results show that DpR is closely related to PFS and OS of NSCLC patients receiving first-line platinum-based chemotherapy (Table 2) (37). Another retrospective analysis conducted by Qing et al. also obtained similar results, in which advanced non-squamous non-small cell lung cancer patients received paclitaxel carboplatin combined with bevacizumab (TCBev) regimen as first-line chemotherapy (44). The greater DpR is, the longer PFS lasts [DpR <30% vs. 30% ≤ DpR <60% vs. DpR ≥60%, PFS (10.6 vs. 8.2 vs. 6.4 months, P<0.001)].

Small cell lung cancer (SCLC) is sensitive to radiotherapy and chemotherapy, and the tumor shrinks rapidly and greatly. In order to verify whether DpR is a predictive factor for survival outcome of patients with SCLC, Long et al. (38) conduct a retrospective analysis of patients with extensive SCLC who received first-line chemotherapy, results indicated that a greater DpR is associated with longer PFS and OS for patients, which proved that DpR is an independent prognostic factor for OS.

**Application of DpR in targeted therapy of lung cancer**

Targeted therapies significantly prolong survival time and improve life quality of lung cancer. For example, the median PFS was 18.9 months and median OS was 38.6 months with osimertinib in untreated, EGFR-mutated advanced NSCLC (45); the median PFS were 34.8 months with alectinib in untreated ALK-positive advanced NSCLC (46).

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**Table 1 Application of DpR in colorectal cancer**

| Patients | Regimen | Sample size | Outcomes | References |
|----------|---------|-------------|----------|------------|
| KRAS WT mCRC | Chemotherapy + cetuximab | 841 | Median DpR: FOLFIRI + cetuximab: 50.9%, FOLFOX4 + cetuximab: 57.9%; higher DpR with longer PPS | (7) |
| KRAS WT mCRC | Chemotherapy + cetuximab | 54 | Median DpR 56.3%, correlation between DpR and outcomes (OS: rs=0.314, P=0.027; PPS: rs=0.366, P=0.017) | (19) |
| KRAS WT mCRC | Chemotherapy + cetuximab | 92 | Median DpR 50.4%, correlation between DpR and outcomes (PFS: rs=0.56, P<0.0001; OS: rs=0.39, P=0.0090) | (18) |
| KRAS WT mCRC | Chemotherapy + cetuximab | 76 | Median DpR 52%, DpR correlated with OS and PFS | (20) |
| KRAS WT mCRC | Chemotherapy + cetuximab | 188 | Median DpR: 48.9%, DpR correlated (P<0.0001) with OS | (21) |
| mCRC | Second-lineChemotherapy + cetuximab | 112 | Median DpR: 56.3%, correlation between DpR and outcomes (OS: rs=0.51, P<0.001; PFS: rs=0.54, P<0.001) | (22) |
| RAS WT mCRC | Chemotherapy + panitumumab | 460 | DpR ≥30% vs. <30%: mPFS (11.9 vs. 3.8 months, HR 3.25 (95% CI, 2.62–4.04); P<0.0001); mOS (30.3 vs. 9.4 months, HR 3.24 (95% CI, 2.59–4.05); P<0.0001) | (23,24) |
| KRAS WT mCRC | Chemotherapy + panitumumab | 170 | DpR ≥30% vs. <30%, mPFS [13.0 vs. 7.4 months, HR 2.80 (95% CI, 1.86–4.23); P<0.0001]; mOS (median 37.4 vs. 17.3 months, HR 3.08 (95% CI, 2.01–4.71); P<0.0001) | (23,25) |
| KRAS WT mCRC | Chemotherapy + panitumumab | 53 | median DpR 48%, correlation between DpR and outcomes (PFS: Spearman Coefficient: =0.53, P<0.0001) (OS: Spearman Coefficient=0.51, P<0.0002) | (23,26) |
| mCRC | Chemotherapy | 156 | Median DpR 44.2%, DpR ≥45% vs. <45%, mPFS (16.4 vs. 8.1 months, P=0.006); mOS (58.6 vs. 30.9 months, P=0.041) | (27) |
| mCRC | Chemotherapy | 242 | median DpR 38.5%, DpR ≥60% vs. <60%, PFS (11.6 vs. 4.8 months, P<0.001); PPS (18.4 vs. 10.1 months, P<0.001); OS (31.6 vs. 17.2 months; P<0.001) | (28) |
| mCRC | Chemotherapy + bevacizumab | 508 | median DpR 38.5%, DpR ≥60% vs. <60%, PFS (10.6 vs. 8.2 vs. 6.4 months, P<0.001)] | (29) |
| mCRC | Chemotherapy + bevacizumab | 508 | median DpR 48%, correlation between DpR and outcomes (PFS: Spearman Coefficient: =0.53, P<0.0001) (OS: Spearman Coefficient=0.51, P<0.0002) | (23,26) |
| mCRC | Second-lineChemotherapy | 112 | FOLFIRI+cetuximab, correlation between DpR and outcomes | (22) |
| mCRC | Chemotherapy | 54 | DpR ≥30% vs. <30%: mPFS (11.9 vs. 3.8 months, HR 3.25 (95% CI, 2.62–4.04); P<0.0001); mOS (30.3 vs. 9.4 months, HR 3.24 (95% CI, 2.59–4.05); P<0.0001) | (23,24) |
| mCRC | Chemotherapy + panitumumab | 460 | DpR ≥30% vs. <30%, mPFS [13.0 vs. 7.4 months, HR 2.80 (95% CI, 1.86–4.23); P<0.0001]; mOS (median 37.4 vs. 17.3 months, HR 3.08 (95% CI, 2.01–4.71); P<0.0001) | (23,25) |
| mCRC | Chemotherapy + panitumumab | 53 | median DpR 48%, correlation between DpR and outcomes (PFS: Spearman Coefficient: =0.53, P<0.0001) (OS: Spearman Coefficient=0.51, P<0.0002) | (23,26) |
| mCRC | Chemotherapy | 156 | Median DpR 44.2%, DpR ≥45% vs. <45%, mPFS (16.4 vs. 8.1 months, P=0.006); mOS (58.6 vs. 30.9 months, P=0.041) | (27) |
| mCRC | Chemotherapy | 242 | median DpR 38.5%, DpR ≥60% vs. <60%, PFS (11.6 vs. 4.8 months, P<0.001); PPS (18.4 vs. 10.1 months, P<0.001); OS (31.6 vs. 17.2 months; P<0.001) | (28) |
| mCRC | Chemotherapy + bevacizumab | 508 | median DpR 48%, correlation between DpR and outcomes (PFS: Spearman Coefficient: =0.53, P<0.0001) (OS: Spearman Coefficient=0.51, P<0.0002) | (23,26) |
| mCRC | Chemotherapy | 156 | Median DpR 44.2%, DpR ≥45% vs. <45%, mPFS (16.4 vs. 8.1 months, P=0.006); mOS (58.6 vs. 30.9 months, P=0.041) | (27) |
| mCRC | Chemotherapy | 242 | median DpR 38.5%, DpR ≥60% vs. <60%, PFS (11.6 vs. 4.8 months, P<0.001); PPS (18.4 vs. 10.1 months, P<0.001); OS (31.6 vs. 17.2 months; P<0.001) | (28) |
| mCRC | Chemotherapy + bevacizumab | 508 | median DpR 38.5%, DpR ≥60% vs. <60%, median PFS (11.6 vs. 4.8 months, P<0.001); median OS (31.6 vs. 17.2 months; P<0.001) | (28) |
| mCRC | Chemotherapy + bevacizumab | 508 | median DpR 48%, correlation between DpR and outcomes (PFS: Spearman Coefficient: =0.53, P<0.0001) (OS: Spearman Coefficient=0.51, P<0.0002) | (23,26) |
A retrospective research about EGFR-TKI and the other research about ALK-TKI for advanced NSCLC patients, these patients were classified into four groups according to the percentage of maximal tumor shrinkage (Q1=1–25%, Q2=26–50%, Q3=51–75%, and Q4=76–100%). Q0 had no shrinkage. The two trials suggested that DpR may be an additional outcome measure for clinical trials. On the contrary, other researches showed that DpR cannot be used as a prognostic indicator for targeted therapy of lung cancer.

Wu et al. (41) analyzed patients with advanced EGFR mutation-positive NSCLC enrolled in first line gefitinib and afatinib trials. The study defined

| Patients | Regimen | Sample size | Outcomes | References |
|----------|---------|-------------|----------|------------|
| Stage IIIB to IV NSCLC | Carboplatin + nab-paclitaxel/solvent-based paclitaxel | 959 | Quartiles based on DpR (NTR: had no shrinkage, Q1:=0% to 25%, Q2:=25% to 50%, Q3:=50% to 75%, Q4:=75%); NTR vs. Q1 vs. Q2 vs. Q3 vs. Q4 vs. Q5, mPFS (2.7 vs. 5.6 vs. 6.9 vs. 8.3 vs. 10.9 months, HR: 0.22, 0.17, 0.13, 0.08, P<0.00001); mOS (4.8 vs. 10.4 vs. 14.5 vs. 19.3 vs. 23.5 months, HR: 0.39, 0.27, 0.20, 0.15, P<0.0001) | (37) |
| No-Squamous NSCLC | Paclitaxel + carboplatin + bevacizumAb | 80 | DpR:30% vs. 30%≤ DpR <60% vs. DpR ≥60%; PFS (10.6 vs. 8.2 vs. 6.4 months, P<0.001) | (37) |
| extensive SCLC | Chemotherapy | 50 | Quartiles based on DpR (Q1=0–25%, Q2=26–50%, Q3=51–75%, Q4=76–100%); Q1 vs. Q2 vs. Q3 vs. Q4, mPFS (4.3 vs. 9.3 vs. 8.6 vs. 8.9 months, P<0.0001); mOS (7.2 vs. 13.6 vs. 12.6 vs. 13.7 months, P<0.0001); correlation between DpR and outcomes (PFS: rs=0.67; OS: rs=0.64) | (38) |
| Locally advanced NSCLC or IV NSCLC (ALK+) | ALK inhibitor | 305 | Quartiles based on DpR (NTR: had no shrinkage, Q1=1–25%, Q2=26–50%, Q3=51–75%, Q4=76–100%); correlation between DpR and outcomes, HR (95% CI) for PFS (Q1 to Q4 compared to NTR): 0.19 (0.09, 0.40), 0.11 (0.06, 0.24), 0.05 (0.03, 0.11), 0.03 (0.02, 0.07); for OS (Q1 to Q4): 0.94 (0.34, 2.61), 0.56 (0.21, 1.51), 0.28 (0.11, 0.73), 0.05 (0.01, 0.28) | (39) |
| Advanced NSCLC | EGFR-TKI | 265 | Quartiles based on DpR (Q1=1–25%, Q2=26–50%, Q3=51–75%, Q4=76–100%); HR (95% CI) for PFS (Q2 to Q4 compared to Q1): 0.58 (0.42, 0.80), 0.49 (0.35, 0.69), 0.33 (0.22, 0.50) | (40) |
| Advanced NSCLC | EGFR-TKI | 98 | DpR not associated with outcomes, high vs. low shrinkage in CR+PR for PFS: Week 8: HR 1.30 (95% CI, 0.71, 2.38), P=0.39; Week 16.5: HR 0.99 (95% CI, 0.60, 1.63), P=0.956; Week 56: HR 1.02 (95% CI, 0.48, 2.18), P=0.958; high vs. low shrinkage in CR+PR for OS: Week 8: HR 1.31 (95% CI, 0.68–2.55), P=0.421; Week 16.5: HR 1.36 (95% CI, 0.77–2.41), P=0.289; Week 56: HR 1.02 (95% CI, 0.55–1.91), P=0.94 | (41) |
| Advanced NSCLC | EGFR-TKI | 1,081 | DpR at week 6 not associated with outcomes, PFS: HR 0.96 (95% CI, 0.70–1.30), P=0.78; OS: HR 0.83 (95% CI, 0.60–1.15), P=0.26 | (42) |
| IIIB or IV NSCLC PD-1 inhibitor | PD-1 inhibitor | 355 | Quartiles based on DpR (NTR: had no shrinkage; Q1=1–25%, Q2=26–50%, Q3=51–75%, Q4=76–100%); correlation between DpR and outcomes, HR (95% CI) for PFS (Q1 to Q4 compared to NTR): 0.30 (95% CI, 0.22–0.41), 0.22 (95% CI, 0.15–0.32), 0.09 (95% CI, 0.06–0.15), 0.07 (95% CI, 0.03–0.12); HR for OS (Q1 to Q4): 0.52 (95% CI, 0.37–0.74), 0.47 (95% CI, 0.30–0.74), 0.07 (95% CI, 0.03–0.18), 0.14 (95% CI, 0.06–0.32) | (39) |
| Advanced NSCLC | Nivolumab | 31 | DpR>10% vs. <10% at weeks 8 to 12: PFS:16.6 vs. 5.1 months, P<0.001 | (43) |

Table 2 Application of DpR in lung cancer
tumor shrinkage $\geq$30% as responders, then responders were categorized by the median DpR (49.5%) into high and low shrinkage groups. No differences in PFS and OS were detected between the two groups at weeks 8, 16.5, and 56. It holds the view that DpR in responders was not predictive for PFS or OS. Lee et al. (42) analyzed data from 5 randomized trials (EURTAC, IPASS, ENSURE, LUX-Lung 3, and LUX-Lung 6 (47-51), and they also found that DpR was not associated with PFS and OS. The predictive role of DpR is still controversial in the application of targeted therapy for lung cancer.

**Application of DpR in immunotherapy of lung cancer**

Immune checkpoint inhibitors (ICIs) present a significant progress in oncology. Tumors respond differently to immunotherapies compared with cytotoxic drugs and targeted therapies, patterns of response and progression of ICIs differ from those seen with chemotherapeutic agents, raising questions about the assessment of changes in tumor burden (52-55). ORR and DCR defined by RECIST1.1 may have some deficiencies in evaluating the efficacy of immunotherapy.

In 2017, DpR was firstly applied to evaluate the prognosis of patients with stage IIIIB to IV NSCLC received ICIs. An exploratory analysis of data on 2 RCTs on PD-1 inhibitors indicated that patients with 50% tumor shrinkage may be the cut-off value for predicting benefits of immunotherapy (39). A report on the relationship between early DpR and survival outcomes in advanced NSCLC patients treated with nivolumab, indicated that patients whose DpR $\geq$10% at the first evaluation (8-12 weeks after starting nivolumab) have longer PFS (DpR $\geq$10% vs. DpR <10%, PFS: 16.6 vs. 5.1 months, P<0.001). They proposed that the early tumor response classification based on the degree of DpR may not accurately predict the long-term prognosis of NSCLC patients treated with nivolumab, and the depth of tumor remission may have a good application prospect in clinical practice (43).

DpR, as a predictor in targeted therapy and immunotherapy, is still controversial. The main reasons are as follows. Firstly, the patients included in the studies, Wu et al.’s study included patients with advanced EGFR mutation-positive NSCLC enrolled in first-line gefitinib and afatinib trials (41). In Lee et al.’s study (42), patients who died or had disease progression measured by RECIST prior to or at 6 weeks were excluded. Besides, the status of gene may have influence on patients with advanced NSCLC treated with EGFR-TKI, like the TP53. Second, the treatments were distinctive, afatinib have greater affinity for EGFR tyrosine kinase domain compared to first-generation EGFR-TKIs and its irreversible pan-ErbB inhibitory property can lead to the different response pattern. Third, the design of the study, for example, Wu et al. observed the correlation between DpR and prognosis in patients who reached PR, not all patients. In addition, the number of patients included is different, and small sample size is heterogeneous for statistical analysis. There are only 2 studies about the application of DpR in immunotherapy of lung cancer, new criteria for immunotherapy were developed, such as irRECIST, irRC, and irRECIST (53,56,57), these results needed further exploration to confirm. The correlation between DpR and OS may be affected by the subsequent treatment (58). More clinical trials are required to confirm the predictive value of DpR.

**Application of DpR in gastric cancer**

The incidence rate of gastric cancer ranks fifth among malignant tumors and the mortality rate of cancer ranks third worldwide. Human epidermal growth factor receptor 2 (HER2) is an important biomarker and key driver of tumorigenesis in gastric cancer (59). For HER2 positive advanced gastric cancer (AGC) patients, chemotherapy combined with trastuzumab is currently the recommended standard treatment (60).

There are 3 retrospective studies of HER2 positive (HER2+) AGC patients received chemotherapy with trastuzumab, which showed that DpR can be a significant predictor for HER2+ AGC patients (61-63). The DpR cut-off value ranged from 44% to 50% in these studies, these patients were grouped according to the DpR cut-off value, and the results showed that the prognosis of DpR $\geq$ cut-off value group was better, which confirmed the predictive value of DpR in the first-line treatment by trastuzumab combined with chemotherapy for AGC patients. Lee et al. (61) retrospectively analyzed 368 CT examinations of 61 patients with AGC. According to Youden’s J index, the optimal cut-off value of DpR was determined to be 45%. The analysis showed that PFS and OS of patients with DpR $\geq$45% were longer (Table 3). Predictive value of DpR is associated with targeted drugs and chemotherapy regimens (8,65), Kadowaki et al. (62) didn’t publish chemotherapy regimen and HER2 mutation status, which may affect the research.
In recent years, studies on the second-line therapy of gastric cancer have shown that the second-line therapy can prolong the survival of patients (66–68). Lee et al. (61) further analyzed subgroups of patients receiving second-line chemotherapy, indicating that DpR was correlated with PPS (HR =0.84; 95%CI, 0.712 to 0.999). Osumi et al. (63) collected the clinical data of 286 patients with AGC who received first-line therapy, in which 186 patients with Her2+ AGC received chemotherapy combined with trastuzumab, and 100 patients with Her2 negative (Her2) received S-1 plus oxaliplatin (SOX) or S-1 plus cisplatin (SP). They found that the DpR and survival time in Her2+ group was better than that in the Her2 negative group. In the Her2+ group, DpR was associated with PFS and OS. In the Her2− group, the median value of DpR was 24%. DpR ≥24% was also associated with significantly longer PFS than DpR <24%, while DpR was not associated with OS (DpR ≥24% vs. <24%, PFS: 7.6 vs. 4.5 months, HR 0.63, P=0.01; OS: 14.8 vs. 12.2 months, HR 0.87, P=0.48). The G-SOX Phase III clinical trial (69) included 632 patients who received the first-line SOX regimen and CS regimen. The relationship between DpR and prognosis was analyzed. The results showed that DpR was correlated with PFS and OS (64), which was different from the results of Osumi et al.’s.

In the gastric cancer, DpR may become a new predictor for efficiency. However, the predictive value of DpR is not sure, which may be related to other factors, for example, the mutation status of HER2, treatment methods, and so on. At present, the ICI treatment in GC provided modest survival benefit, further research is needed in the future.

Table 3 Application of DpR in gastric cancer

| Patients                              | Regimen                           | Sample size | Outcomes                                      | References |
|---------------------------------------|------------------------------------|-------------|-----------------------------------------------|------------|
| Advanced gastric cancer (HER2+)       | Chemotherapy + Trastuzumab         | 61          | DpR ≥45% vs. <45%, mPFS [9.0 vs. 6.3 months, HR =0.608 (95% CI: 0.335–1.104), P=0.102]; mOS (23.5 vs. 13.1 months, HR =0.441 (95% CI: 0.203–0.955), P=0.038) (61) |
| Advanced gastric cancer (HER2+)       | Chemotherapy + Trastuzumab         | 57          | Median DpR 56.8%, DpR ≥50% vs. DpR <50%, mPFS (9.8 vs. 4.1 months, P<0.001); mOS (24.7 vs. 12.8 months, P<0.001) (62) |
| Advanced gastric cancer (HER2+, n=186, HER2-, n=100) | Chemotherapy + Trastuzumab         | 286         | Her2+: Median DpR 44%; DpR ≥44% vs. <44%, PFS: 14 vs. 5.2 months, HR: 0.22, P<0.0001; OS: 29.7 vs. 11.5 months, HR: 0.24, P<0.0001; Her2−: Median DpR, 24%; DpR ≥24% vs. <24%, PFS: 7.6 vs. 4.5 months, HR 0.63, P=0.01; OS: 14.8 vs. 12.2 months, HR 0.87, P=0.48 (63) |
| Advanced gastric cancer               | Chemotherapy                       | 632         | DpR cutoff values 36.7% for PFS, 40.0% for OS, DpR moderately predicted PFS [Cr index 0.697 (95% CI, 0.678–0.717]) and OS [Cr index 0.644 (95% CI, 0.622–0.663)] (64) |

Application of DpR in other solid tumors

DpR is rarely reported in other solid tumors. A study analyzed the evaluation value of DpR in patients with BRAF V600 mutant metastatic melanoma who received vemurafenib or without Cobimetinib. The study collected data from 4 clinical trials (brim-2, brim-3, brim-7 and coBRIM), which showed that higher DpR is associated with longer survival, and supported DpR as a new measure in addition to traditional clinical prognostic variables (70). In 2016, Kaga et al. (71) firstly reported the application of DpR to 59 advanced pancreatic cancer (APC) patients receiving oxaliplatin, irinotecan, fluorouracil and calcium folinate (FOLFIRINOX). They found that DpR was significantly but weakly associated with OS (rs=0.18, P=0.017) and was not associated with PFS. In 2018, Vivaldi et al. (72) estimated the prognostic role of DpR in metastatic PC treated with FOLFIRINOX or gemcitabine with nab-paclitaxel (GemNab). The study showed that median DpR was 27.5%, DpR ≥27.5% was significantly associated with better PFS (9.0 vs. 6.7 months, P<0.001) and OS (14.3 vs. 11.1 months, P=0.031). DpR could be a favorable efficacy outcome measure in advanced PC treated with first-line combination chemotherapy. Che’s study about HER2-positive metastatic breast cancer treated with trastuzumab, they suggested that DpR could be used as predictors of clinical outcomes in metastatic breast cancer patients treated with trastuzumab-based regimens in the first-line setting. They suggested the cutoff value of DpR ≥40% to distinguish patients with favorable clinical outcomes (73).

At present, there is still a lack of application of DpR in
other solid tumors, such as liver cancer, esophageal cancer and cervical cancer. The predictive value of DpR in more solid tumors can be further explored in the future.

**Discussion and conclusions**

DpR has been explored in the evaluation of the efficacy of various solid tumors. DpR is a valuable surrogate endpoint for mCRC patients, both in mCRC patients received first-line cetuximab, panitumumab or bevacizumab-based chemotherapy and in mCRC patients received second-line cetuximab-based chemotherapy. In addition, DpR could be an outcome measure in metastatic breast cancer, metastatic melanoma and APC in in existing research. DpR is a continuous metric, which could avoid the information loss due to dichotomization of responses and might provide an earlier indications of drug activity than time to PFS or OS, representing a more powerful and informative metric. However, the predictive value of DpR is still uncertain in the research of lung cancer and gastric cancer. Unified application standard hasn't been formed, and there are still some disputes and limitations. Firstly, some researches (74-76) reported that bias occurs when patients are categorized into good and bad responder groups at baseline and then survival in these groups is compared. There is a time window for tumor shrinkage. A longer time for the occurrence of a larger DpR, which may prolong the PFS and OS of the patient. In addition, DpR is based on the measurement of tumor diameter, but the growth and remission of the tumor are not symmetrical. The imaging changes cannot fully reflect the state of the tumor. The author thinks that the time-dependent bias needs to be taken into account in future research. Secondly, researches on DpR in solid tumors is based on the data obtained by retrospective analysis which have many interferences, so prospective research is urgently needed. In addition, prognosis for tumor is relate to many factors, such as tumor cell's biological behaviors, status of some biomarkers, and so on. The ability of proliferation and invasion decide the speed of tumor growth and tumor heterogeneity. In the era of precision medicine, more and more attention are being paid to be concerned with the molecular level of DNA and epigenetics. DpR cannot be a single predictor for efficacy, we need to consider these factors all together. DpR may be a promising predictor in future clinical trials, DpR needs to be based on these existing prognostic prediction models for larger scale prospective trials and synchronous comparison with Recit1.1 to further explore the value of DpR, to form a perfect application specification, guide clinical work, and improve patient prognosis.

**Acknowledgments**

We thank our friend Qinyi Liao, for her valuable advice and contribution to polish the manuscript.

**Funding** None.

**Footnote**

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2547

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2547). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Xie X, Li X, Yao W. A narrative review: depth of response as a predictor of the long-term outcomes for solid tumors. Transl Cancer Res 2021;10(2):1119-1130. doi: 10.21037/tcr-20-2547