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ORIGINAL ARTICLE

Is there an impact of heart exposure on the incidence of radiation pneumonitis? Analysis of data from a large clinical cohort

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Abstract

Background. The goal of the present study was to determine, in a large clinical cohort, whether incidental radiation exposure to the heart during definitive radiotherapy of inoperable non-small cell lung cancer (NSCLC) detectably increased the risk of radiation pneumonitis (RP) beyond that resulting from radiation exposure to lung. *Material and methods.* Data were analyzed from all patients who received definitive three-dimensional (3D) concurrent radiotherapy or intensity-modulated radiotherapy for the treatment of NSCLC over a 10-year period at our institution, except those who had previous lung cancer or for whom radiation treatment plans were unavailable for calculation of heart and lung dose-volume histograms (DVHs). Parameters computed from heart and lung DVHs included mean lung dose (MLD), effective lung dose computed using volume parameter n = 0.5 (D_{eff}), mean heart dose (MHD), percentage of heart receiving > 65 Gy (V65), and minimum dose to the hottest 10% of heart (D10). Univariate and multivariate normal-tissue complication probability (NTCP) models were used to analyze incidence of Grade ≥ 2 or Grade ≥ 3 RP as a function of these and other parameters. *Results.* The study cohort included 629 patients, with crude rates of Grade ≥ 2 RP and Grade ≥ 3 RP of N = 263 (42%) and N = 124 (20%), respectively. Univariate NTCP models based on dosimetric lung parameters (MLD and D_{eff}) fit the data better than models based on univariate heart parameters (heart D10, heart V65 or MHD). In multivariate modeling, incorporation of heart parameters did not significantly improve the fit of RP risk models based on lung parameters alone ($p > 0.38$ in each case). *Conclusions.* In this large clinical cohort, there was no evidence that incidental heart exposure during radiotherapy of NSCLC had a detectable impact on the occurrence of moderate or severe RP.

Patients with non-small cell lung cancer (NSCLC) who undergo definitive treatment with radiotherapy, with or without concurrent chemotherapy, are at risk of developing radiation pneumonitis (RP), a potentially severe and sometimes fatal complication of thoracic irradiation. The risk of RP is known to depend on the extent of incidental radiation exposure to normal lung tissue located outside the target volume, and the association between mean lung dose (MLD) and incidence of RP is well established [1].

Experimental studies in animal models have clearly shown that heart irradiation can influence the occurrence of radiation-induced lung injury. For example, in studies of rat lung, van Luijk et al. demonstrated significant differences in breathing rates [2,3] and morphology [4] after large, single radiation doses to the lung, depending on whether or not the heart was included in the treatment field.

Conflicting results have been reported regarding the impact of incidental heart irradiation on RP occurring after clinical radiotherapy of patients with NSCLC. In univariate analyses of data from 78 patients, Yorke et al. found no association between severe RP and mean heart dose (MHD), maximum heart dose, or heart D05, where Dx represents the minimum dose to x% of the organ receiving highest doses [5]. Dang et al. found an association between heart parameters, including MHD, in univariate analyses of both Grade ≥ 2 and Grade ≥ 3 RP in a cohort of 176 patients, but significance was not

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maintained in multivariate analyses [6]. Consistent with these findings, a meta-analysis of five studies reporting RP risk in patients with left versus right lung involvement found no evidence for an increased risk of RP among patients with left-sided tumors, as might be expected if there were an impact of heart exposure on lung toxicity [7]. However, Huang et al. reported a heart effect in both univariate and multivariate analyses of RP in a cohort of 219 patients [8]. In univariate analyses of their data, heart parameters such as V65, the proportion of heart exposed to at least 65 Gy, were more strongly associated with RP incidence than were lung parameters. In multivariate analyses, their best-fitting model for predicting RP risk included both heart and lung parameters, specifically heart D10, lung D35, and maximum lung dose [8].

The goal of the present study was investigate the impact of incidental heart exposure on the incidence of RP in a large clinical cohort of NSCLC patients treated at our institution with definitive radiotherapy, with or without chemotherapy. Analysis of this large cohort, treated over a 10-year period with a variety of different radiation treatment designs, was expected to provide important evidence for or against a role of heart exposure in the risk of RP during routine clinical practice.

Material and methods

Patient cohort

The data analyzed here were extracted from our large clinical database consisting of all NSCLC patients receiving radiotherapy at our institution since the introduction of three-dimensional conformal radiotherapy (3D-CRT). Patients included in the present analysis were those who: 1) received 3D-CRT or intensity-modulated radiotherapy (IMRT) as definitive treatment (i.e. excluding patients treated with protons, stereotactic radiotherapy or post-surgical radiotherapy); 2) started radiotherapy at least one year prior to initiation of our study; 3) had no previous lung cancer; and 4) had radiation treatment plans retrievable from the institutional archives for extraction of dosimetric information describing radiation exposure to heart and lung. Retrospective analyses of these data were approved by our institutional review board and informed consent was waived.

Dose-volume data

The heart was contoured as a solid organ from the apex to the inferior border of the right pulmonary artery, and normal lung was contoured as a single organ, excluding bronchi and gross tumor volume. Radiation doses to heart and lung were computed using the superposition-convolution algorithm, which accounts for tissue inhomogeneities. Dose-volume histograms (DVHs) for were computed using 0.1-Gy dose bins. DVHs were based on physical dose, not adjusted for differences in dose per fraction, based on our previous finding of a lack of fractionation effect for the severe pneumonitis endpoint [9].

Pneumonitis endpoint

RP was graded retrospectively based on patient records and radiographic images, and was scored using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/reporting/ctc.html). Patients were examined weekly during radiotherapy and 4–6 weeks after completion of treatment. They were then followed every three months for three years and every six months thereafter, unless they had symptoms that required immediate examination or intervention. Radiographic examination by chest x-ray or computed tomography (CT) scan was performed at each follow-up visit.

The primary endpoint for the present analysis was severe (Grade ≥ 3) RP, corresponding to symptoms that interfere with activities of daily living (ADL). Subsequently, Grade ≥ 2 RP was also analyzed; Grade 2 RP corresponds to symptomatic RP that does not interfere with ADL. Time to RP was computed from the start of radiotherapy and was censored at last follow-up or at time of local recurrence, if any, to ensure that lung symptoms could be clearly attributed to radiation-induced toxicity.

Statistical methods

Univariate analyses of RP risk were performed using the probit model, for consistency with the Lyman-Kutcher-Burman (LKB) normal-tissue complication probability (NTCP) model [10,11]. Computed parameters for each univariate model were D_{50} (respectively, V_{50}), representing the value of a dosimetric (respectively, volumetric) covariate corresponding to a 50% complication rate, and m, a parameter inversely related to the slope of the response curve relating the covariate to NTCP.

Univariate lung factors considered were MLD and effective lung dose D_{eff}, which requires choice of a volume parameter, n [12]. Here, the value $n = 0.5$ was used, which weights high doses more heavily than does mean dose [13]. The latter choice was based on our recent studies indicating that D_{eff} for lung computed using $n = 0.5$ is more strongly associated with RP risk than is MLD [9,14,15].

Multivariate modeling was performed using the probit model and the logistic model. Consistent with

the best-fitting model identified by Huang et al. [8] for RP requiring medical intervention, the factors included in the multivariate logistic model were lung D35, maximum lung dose, and heart D10.

NTCP models were fitted to data by maximum likelihood analysis using a mixture model approach in which the event times were taken into account [14,16]. A lognormal density function was used to describe the distribution of RP event times, as described previously [14,15]. Nested model fits were compared using the likelihood-ratio test. Non-nested models were compared using the Akaike Information Criterion (AIC) [17]. Details regarding models used, parameter estimates obtained, 95% profile-likelihood confidence intervals, and comparisons between models are presented in the Supplementary material, available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2013.831185.

To plot the incidence of severe RP versus MLD or D_{eff}, patients were sorted by the dosimetric quantity of interest and divided into approximately equal subgroups. The method of Kaplan and Meier (KM) was used to compute the incidence of RP in each subgroup as 1 minus the KM estimate of freedom from RP at 12 months, with standard error computed using the method of Greenwood [18]. To illustrate the effect of taking into account an additional dosimetric quantity representing heart dose, each of the patient subgroups described above was divided in half according to the magnitude of heart dose, and KM estimates of RP at one year were computed separately for each half.

A sample power calculation was performed to explore the magnitude of the heart effect that should have been detectable in our study if heart exposure does contribute to RP risk. For the calculation, RP risk was assumed to depend on MLD and heart D10, with the additional risk resulting from each 1 Gy increment in heart D10 expressed in terms of the equivalent increase in MLD that would correspond to the same increase in NTCP in the absence of heart exposure. The power calculation was performed using numerical simulations with 1000 iterations per scenario considered.

Results

There were 629 patients in our clinical database meeting the inclusion criteria for the current study. Clinical and treatment-related characteristics of patients in the study cohort are listed in Table I. Median follow-up, measured from the start of radiotherapy, was 19 months (range 1–133 months), and median overall survival 20 months.

The crude incidence of RP was N = 139, N = 110, N = 7, and N = 7 for Grades 2–5, respectively.

Table I. Patient characteristics ($N = 629$).

Factor	Number of patients (%)
Sex	
Female	304 (48)
Male	325 (52)
Age (years)	Median 64 (range 33–92)
Smoking status	
Current smoker	162 (26)
Former smoker	419 (67)
Non-smoker	48 (8)
KPS	
90	163 (26)
80	338 (54)
70	97 (15)
60	30 (5)
50	1 (< 1)
COPD	
No	467 (74)
Yes	162 (26)
Histology	
Adenocarcinoma	226 (36)
Squamous cell carcinoma	193 (31)
NSC NOS	207 (33)
Large cell	1 (< 1)
Unknown	1 (< 1)
Clinical stage	
IA	38 (6)
IB	45 (7)
IIA	9 (1)
IIB	28 (4)
IIIA	213 (34)
IIIB	247 (39)
IV	49 (8)
Induction chemotherapy	
No	333 (53)
Yes	296 (47)
Concurrent chemotherapy	
No	150 (24)
Yes	479 (76)
GTV (cm^3)	Median 111 (range 0.6–1256)
RT modality	
3D-CRT	457 (73)
IMRT	172 (27)
Delivered dose (Gy)	Median 63 (range 50–84)
Fractions per day	
1	568 (90)
2	61 (10)
Fraction size (Gy)	Median 1.8 (range 1.2–2.33)
Mean lung dose (Gy)	Median 20.1 (range 3.6–31.9)
Lung D_{eff} ($n = 0.5$) (Gy)	Median 30.9 (range 10.9–42.5)
Mean heart dose (Gy)	Median 19.2 (range < 0.1–55.4)
Heart D10 (Gy)	Median 58.7 (range 0.3–79.9)
Heart V65 (%)	Median 3.7 (range 0–47.9)

COPD, chronic obstructive pulmonary disease; D_{eff}, effective dose, computed using volume parameter n = 0.5; D10, minimum dose to the 10% of the organ receiving highest dose; GTV, gross tumor volume; IMRT, intensity-modulated radiotherapy; KPS, Karnofsky performance score; NSC NOS, non-small cell lung cancer not otherwise specified; 3D-CRT, three-dimensional conformal radiotherapy; V65, fraction of the organ receiving > 65 Gy.

Accordingly, the crude incidence of Grade ≥ 2 RP was 42% (N = 263) and of severe (Grade ≥ 3) RP 20% (N = 124). Two cases of severe RP and five

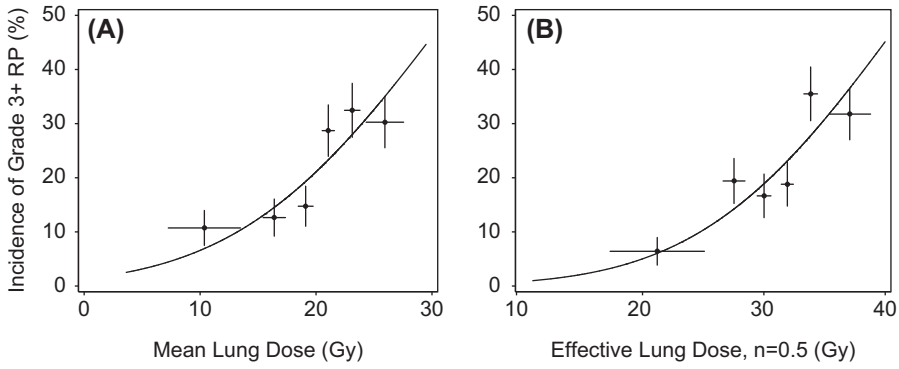

Figure 1. Kaplan-Meier incidence of Grade ≥ 3 radiation pneumonitis (RP) in subgroups of 104–105 patients each, plotted as a function of mean lung dose (MLD) (panel A) or effective lung dose (D_{eff}) computed using volume parameter $n = 0.5$ (panel B). Points are plotted at the mean value of MLD or D_{eff} per subgroup. Horizontal error bars represent ± 1 standard deviation of the dosimetric parameter; vertical errors bars show ± 1 standard error of estimated RP incidence. Solid curves shows the fits of the Lyman-Kutcher-Burman model using volume parameter $n = 1$ (panel A) or $n = 0.5$ (panel B).

cases of Grade 2 RP occurred after local recurrence and were censored for the present analyses.

Figure 1 shows the incidence of severe RP as a function of dosimetric lung parameters alone. The left panel shows RP plotted against MLD, while the right panel shows RP plotted against effective lung dose, D_{eff}, computed using volume parameter $n = 0.5$. In the present cohort, a fit of the LKB model produced the estimate $n = 0.52$ and fit the data significantly better than the model based on MLD ($p = 0.033$). Figure 1 illustrates a marked impact of lung exposure on RP risk.

When heart parameters (heart D10, heart V65 or MHD) were added to the models shown in Figure 1, there was no significant improvement of the model fit ($p > 0.38$ in each case). The lack of improvement observed when heart D10 was added to lung-based risk models is illustrated in Figure 2. If heart exposure contributed significantly to RP risk, one would expect a displacement upward, toward increased RP rates, among patients with higher heart D10 values (red symbols in Figure 2), compared to patients with similar lung exposure but lower heart D10 values (blue symbols). However, there was no evidence of such a trend in these data. Similar results were obtained when MHD and heart V65 were added to the lung-based models. Therefore, we found no evidence of an impact of heart exposure on RP after lung exposure was taken into account.

We next investigated whether occurrence of RP was more significantly associated with univariate dosimetric heart parameters alone than with lung parameters alone. Although heart D10, heart V65 and MHD did demonstrate some degree of association with RP, none of these parameters fit the data better than did MLD or lung D_{eff}, as indicated by the corresponding AIC values. Associations between univariate heart parameters and RP might simply be a consequence of correlation between dosimetric heart parameters (heart D10, V65 and MHD) and dosimetric lung parameters (MLD and

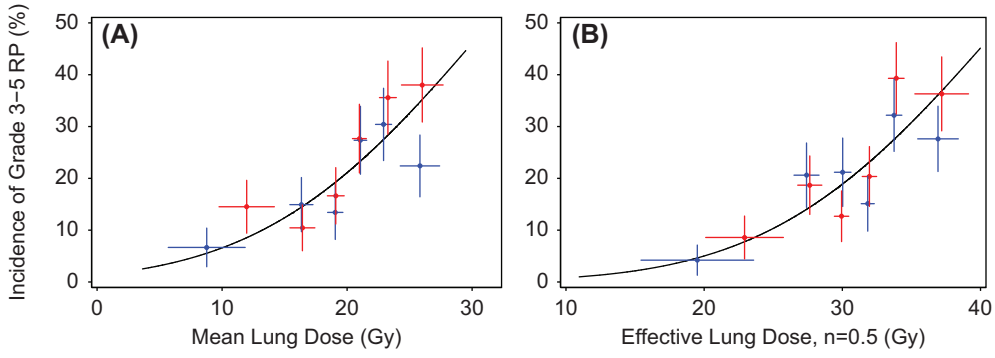

Figure 2. Kaplan-Meier incidence of Grade ≥ 3 radiation pneumonitis (RP) in subgroups of 52–53 patients each, plotted as a function of mean lung dose (MLD) (panel A) or effective dose to lung (D_{eff}) computed using volume parameter $n = 0.5$ (panel B). Patients were first sorted into six subgoups by lung exposure, as in Figure 1, with each group then divided in half according to smaller (blue symbols) versus larger (red symbols) heart D10 values. Points, error bars, and curves are as in Figure 1.

D_{eff}). The significant relationship between one such pair of parameters, MHD and MLD, is illustrated in Figure 3. In fact, each of the heart parameters investigated (D10, V65 and MHD) was strongly correlated with each of the lung parameters ($p < 0.0001$ in all cases).

We also tested the fit of the multivariate logistic model including lung D35 and maximum lung dose as covariates, with and without inclusion of heart D10, to test the significance of heart dose. The coefficient of heart D10 was not significantly different from zero ($p = 0.841$), supporting our conclusion that heart dose does not detectably affect RP risk in the present cohort after lung exposure is taken into account.

Analyses performed using the Grade ≥ 2 RP had the same qualitative results as those described above. Specifically, in multivariate models, no significant impact of heart exposure on RP was detected after lung exposure was taken into account. Furthermore, univariate heart factors did not fit the data as well as lung parameters alone.

The calculation performed to investigate the power of our study to detect an impact of heart exposure on RP risk indicated $>95\%$ power to detect, at a significance level of $p < 0.05$, an impact of heart irradiation equivalent to an increase in MLD as small as 0.02 Gy for each 1 Gy of heart D10. Therefore, our study was extremely well powered to detect even minor effects of heart exposure on the incidence of RP, but no such effect was detected.

Discussion

In the present study, we were unable to find evidence supporting a role of heart irradiation on the risk of moderate or severe RP in data from a large clinical cohort of NSCLC patients ($N > 600$). In particular, we were not able to validate the influence of heart exposure on RP risk reported by Huang et al. [8]. Our results are therefore consistent with other studies indicating a lack of impact of incidental heart exposure on occurrence of RP following clinical radiotherapy of NSCLC [5–7].

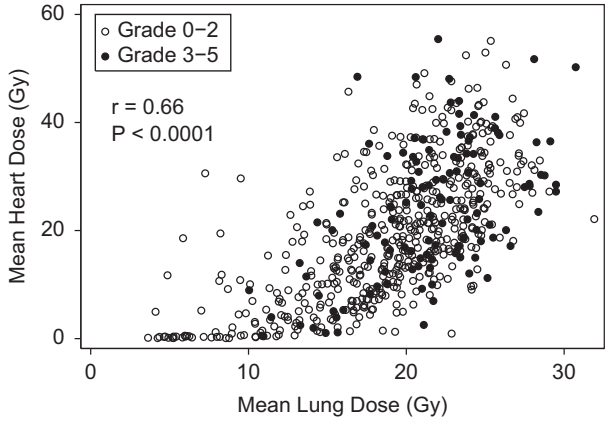

Figure 3. Mean heart dose versus mean lung dose. Solid symbols indicate patients who experienced Grade ≥ 3 radiation pneumonitis ($N = 124/629$). Pearson's correlation coefficient (r) and p-value are shown.

The discrepancy between our results and those of animal studies demonstrating an effect of heart irradiation on lung toxicity [2–4] might perhaps be explained by differences in the lung endpoints considered (breathing rate or morphology vs. RP). It could also be a consequence of the large single radiation doses to substantial portions of lung used in the rodent studies, which are quite different from the dose distributions to normal lung occurring during clinical radiotherapy.

The reason for the discrepancy between our results and those reported by Huang et al. [8] is less clear. The study endpoint likely did not play a role, since their study considered a similar endpoint to ours, namely clinically significant RP requiring administration of steroids or supportive care. The extent of heart irradiation appears to be similar in both studies (Table II), so differences in heart exposure do not seem to account for the conflicting results.

It is well known that various dose-volume parameters assessed from the same patient tend to be highly correlated with one another, so it is possible that heart parameters were selected in the model of Huang et al. because of their correlation with the underlying factors causative for RP. Support for this hypothesis comes from the strong correlations between dosimetric heart and lung factors observed in the present study (c.f. Figure 3) and the fact that

Table II. Summary of dosimetric heart parameters.

	Current study		Study of Huang et al. [8]	
Parameter	Median	Range	Median	Range
D5 (Gy)	64.0	0.2–81.4	47.7	<0.1–84.2
D10 ‘’	58.6	0.2–79.8	40.8	<0.1–81.2
D20 ‘’	41.5	0.1–76.1	29.2	<0.1–75.1
D30 ‘’	24.6	0.1–70.7	21.1	<0.1–72.8
D40 ‘’	14.7	0.1–68.9	14.8	<0.1–71.8
D50 ‘’	7.2	0.1–62.0	10.7	<0.1–67.4
D60 ‘’	3.5	0.1–54.0	7.7	<0.1–65.7
D70 ‘’	2.3	0.1–49.1	5.6	<0.1–64.8
V5 (%)	54.7	0–100	43.8	0–100
V10 ‘’	46.1	0–100	33.4	0–100
V20 ‘’	34.1	0–100	23.4	0–99.9
V30 ‘’	26.3	0–99.9	19.1	0–99.3
V40 ‘’	20.8	0–99.0	13.2	0–97.5
V50 ‘’	15.0	0–62.7	7.4	0–91.9
V60 ‘’	9.1	0–53.6	3.0	0–79.8
V70 ‘’	0	0–33.3	0	0–44.7

Dx, minimum dose to the x% of heart receiving the highest doses; Vx, percent of heart receiving doses of at least x Gy.

their analysis originally included more than 100 dosimetric parameters from which an optimal combination was selected. Furthermore, some of the symptoms leading to a clinical diagnosis of RP, such as dyspnea, are non-specific and may be a consequence of underlying cardiovascular or pulmonary disease, unrelated to radiation exposure. These considerations make RP a statistically *noisy* endpoint, which can make modeling susceptible to detecting chance associations unless the available data are from a very large cohort.

It is possible that our analysis failed to detect an impact of heart irradiation that does in fact affect the risk of RP. This seems unlikely, though, given the large size of our clinical cohort and the number of different ways the effect of heart exposure was incorporated into the data analyses. More importantly, power calculations suggest that we should have been able to detect even a small clinically relevant effect of incidental heart exposure on RP risk in our cohort of >600 patients, treated with a wide range of 3D-CRT and IMRT designs, were such an effect present.

One could ask whether RP risk might be a consequence of exposure to specific anatomic subregions of the heart, such as the right or left ventricles. In the current study, non-contrast CT planning was utilized and therefore the delineation of the ventricles and atria was not feasible, so our study was based on exposure to whole heart, as was the study of Huang et al. [8]. Since dose-volume factors describing exposure to specific organ structures tend to be highly correlated with similar factors computed from the whole organ, we expect that our present analyses would have indicated at least a trend toward an impact of heart irradiation on RP if it were present, even though the entire heart might not have been the relevant structure. In the current study we detected no consistent trend toward an effect of heart exposure on RP incidence, however small. For example, a fit of the multivariate LKB model based on MLD and heart D10 actually found that a slight trend toward *lower* RP risk with increased heart exposure, although the effect was negligible and not significantly different from zero.

We note that the present study did not address the impact on RP on non-dosimetric clinical factors, such as smoking status, that have been shown to play a role in pneumonitis risk [1,14,15]. The possibility remains, therefore, that heart irradiation could potentially increase RP risk in a select subset of patients with particular clinical characteristics.

If it is true that incidental exposure to the heart during 3D-CRT or IMRT of lung cancer does not measurably affect the incidence of RP, it does not mean, of course, that the extent of heart exposure can be ignored during treatment planning. The dose to heart is certainly associated with the risk of potential injury to the heart itself. Long-term adverse cardiac effects have been well documented in survivors of breast cancer and lymphoma [19–21]. Less is known of potential acute and subacute effects of radiation on cardiac function. However, clinical evidence is emerging to suggest that early effects of radiation on cardiac function may not only exist, but may be of clinical significance [22,23].

In summary, the present study of >600 patients finds no evidence that incidental irradiation to heart during radiotherapy of NSCLC has an impact on the risk of RP in the clinical setting. However, the continued study of adverse effects of cardiac irradiation is warranted.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

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