

Scientific Article

Complications From Postmastectomy Radiation Therapy in Patients Undergoing Immediate Breast Reconstruction: A Population-Based Study



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Abstract

Purpose: Previous studies have shown an increase in the number of women electing for immediate breast reconstruction at the time of mastectomy. Although often not known at the time, some of these women will require postoperative radiation therapy. The purpose of this study was to investigate if exposure to radiation therapy after mastectomy with immediate breast reconstruction is associated with an increased risk of further surgery to manage complications arising from radiation.

Methods and Materials: This retrospective, population-based cohort study included all patients who underwent mastectomy with immediate reconstruction from 2007 to 2014 in the province of Ontario, Canada. Exposure to adjuvant radiation therapy was captured using data from Ontario Health. The study outcome was reoperation for breast reconstruction performed during the follow-up window. Cox proportional hazard models were used to assess the effect of radiation therapy exposure on risk of breast reconstruction reoperation.

Results: We identified 2342 patients who underwent mastectomy with immediate reconstruction over an 8-year period in Ontario, of whom 378 (16.1%) underwent adjuvant radiation therapy. Patients who received radiation were significantly more likely to undergo reoperation during follow-up (hazard ratio, 1.76; 95% confidence interval, 1.49-2.08; $P < .0001$). Patients with implant-based reconstructions ($n = 1629$, 69.6%) were not more likely to undergo reoperation than those with flap-based procedures ($n = 713$, 30.4%) (hazard ratio, 1.01; 95% confidence interval, 0.85-1.21; $P = .885$).

Conclusions: Adjuvant radiation therapy initiated after mastectomy with immediate breast reconstruction is associated with an increased risk of additional breast reconstruction surgery, regardless of the type of reconstruction used. Patients with breast cancer who choose to undergo immediate reconstruction after mastectomy should be advised that additional reconstruction procedures may be required.

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The data set from this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). While legal data-sharing agreements between ICES and data providers (eg, health care organizations and government) prohibit ICES from making the data set publicly available, confidential access may be granted to those who meet prespecified criteria, available at www.ices.on.ca/DAS (e-mail: das@ices.on.ca).

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Introduction

A significant shift in immediate breast reconstruction at the time of mastectomy has occurred over the past decade, particularly immediate implant-based reconstruction among younger women with breast cancer.¹⁻⁴ One of the challenges with immediate reconstruction is in predicting the potential need for adjuvant radiation therapy at the time of surgical decision making. Given the reported increased risks of reconstruction failure, capsular contracture, infection, implant exposure, and mastectomy flap necrosis associated with radiation,^{5,6} guidelines such as those from Cancer Care Ontario (now known as Ontario Health) recommend avoiding immediate implant-based reconstruction in patients anticipated to require adjuvant radiation.⁷ However, predicting the potential need for adjuvant radiation therapy preoperatively can be difficult,⁸ and, thus, the challenge to the modern breast surgeon is offering immediate breast reconstruction to appropriate early-stage cancer patients while attempting to avoid immediate implant reconstruction in patients who will require radiation.

Despite efforts to avoid offering immediate reconstruction in patients who may require adjuvant radiation, studies have demonstrated a continued increase in immediate breast reconstruction in this setting.^{5,8} Complication rates following mastectomy with immediate breast reconstruction are estimated to be 27% with a reoperation rate of 6.6%⁹; however, for patients who undergo radiation therapy following reconstruction, there is wide variation in the estimated complication rate,¹⁰⁻¹² with 1 study reporting that major corrective surgery is required in 9% of patients with autologous reconstructions and up to 40% with implant-based reconstructions.¹³ Given findings that suggest patients report high acceptance of immediate breast reconstruction and improved quality of life even when reconstruction is followed by adjuvant radiation therapy,¹⁴ accurate estimates of complication and reoperation rates are needed to ensure patients are fully informed. The primary objective of this study was to review women undergoing immediate breast reconstruction over an 8-year period and compare reoperation rates for complications (hematoma, capsular contracture, infection) between patients who did or did not receive adjuvant radiation.

Methods and Materials

Study design and data sources

This retrospective, population-based cohort study included women who underwent a mastectomy and same day breast reconstruction, for any indication, in the

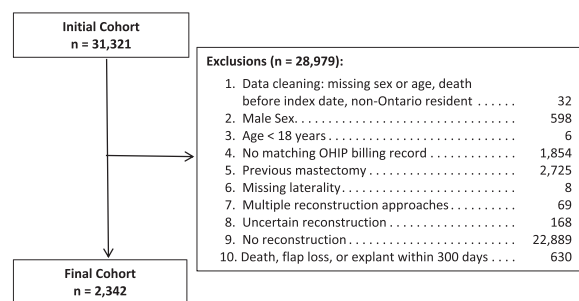


Figure 1 Cohort build flow diagram.

province of Ontario, Canada (population approximately 13 million),¹⁵ from January 1, 2007, to December 31, 2014. We began with a cohort designed for a previous study⁸ that included women with mastectomy. This cohort excluded non-Ontario residents, pediatric patients, and those with missing or invalid age, sex, or mastectomy laterality. Patients who had undergone a prior mastectomy, did not have an associated physician billing record, or had an uncertain reconstruction status or approach were also excluded. For the current study, we additionally excluded patients without immediate breast reconstruction as well as those who died or experienced flap loss or explantation before the start of follow-up period (see exposure definition in the Variable Definitions section). The number of patients excluded at each step of the cohort build is presented in Fig. 1.

All residents in Ontario have access to universal health care, and all hospital and physician-based health care encounters are captured in administrative databases. Data sets used in the current study (see Table E1) were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences, Western University. The Institute for Clinical Evaluative Sciences is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act, and, as a result, approval for this study from a research ethics board was not required. Reporting of this study follows the RECORD statement.¹⁶

Variable definitions

Breast reconstruction approach was defined as implant-based, flap-based, or a combination of the 2 using Canadian Classification of Health Intervention codes (see Table E2 for a complete list of all study codes). Additional baseline variables include patient age, rural residence, neighborhood income quintile (adjusted for household size and housing costs), expected resource utilization, history of lupus, prior lumpectomy, history of breast-conserving therapy (lumpectomy with evidence of radiation therapy within 1 year), and breast cancer diagnosis (as well as stage and time from diagnosis to mastectomy). Expected resource utilization was derived from the Johns

Hopkins University Adjusted Clinical Group case-mix system's Resource Utilization Bands (RUB)¹⁷ and summarized as low (RUB = 0-3), moderate (RUB = 4), and high (RUB = 5). We also captured institution teaching status (academic vs community), surgeon experience (years since medical school graduation), and surgeon annual breast surgery volume (based on all breast-related procedures billed during the same year).

Exposure to adjuvant radiation therapy was defined as the date of the third visit for radiation therapy recorded in the Cancer Activity Level Reporting database. The third visit was selected because the first and possibly second visits likely represent consultation or planning visits rather than radiation delivery. As part of Cancer Care Ontario (Ontario Health), the Activity Level Reporting database captures radiation and systemic therapy services and outpatient oncology clinic visits for every patient diagnosed with a malignant neoplasm in Ontario.¹⁸ To be considered exposed, all 3 visits had to occur within 10 months of mastectomy. The 10-month threshold was chosen after reviewing the data, which showed that a large number of patients underwent revision surgery within the first few months after the initial reconstruction; based on clinical experience, the majority of these procedures were likely related to 2-stage reconstructions or surgical complication.

We also found that the 10-month threshold aligned well with radiation therapy provision, in that most patients who would receive radiation therapy began treatment within this period. Given that patients who require postmastectomy radiation are typically node positive, many will also require adjuvant chemotherapy, meaning that it may be up to 6 months after surgery before radiation is delivered and up to 8 months if delays are planned between treatments. After 10 to 12 months after surgery, delivery of radiation will have reduced efficacy. Therefore, radiation delivered more than 1 year after surgery was considered salvage/recurrent treatment. Patients with metastases were excluded from this study. The standard radiation protocol used to treat patients with breast cancer postmastectomy during the period of this study was 50 Gy in 25 fractions with consideration for boost to regional nodal basins for patients with 4+ nodes or in patients with stage 3, triple-negative molecular subtype, medial tumors, or young age less than 50 years.¹⁹ Given the more recent European guidelines,²⁰ regimens have since adopted these changes, and most patients are receiving 40 Gy in 15 fractions.

The study outcome was a reoperation for breast reconstruction as a measure of complications significant enough to warrant surgical intervention, including revisional surgeries such as capsulotomy or capsulectomy for contracture, performed more than 10 months after the initial surgery. Reconstructions on the contralateral side were not captured. Revision surgeries that occurred

within the first 10 months were captured as early reoperations, nearly all of which occurred before radiation therapy was initiated. Follow-up time ranged from 3 years, 8 months to 11 years, 8 months.

Statistical analysis

Differences in baseline characteristics between patients who did and did not receive radiation therapy were evaluated using standardized differences, with values greater than 0.10 interpreted as a potentially meaningful between group difference.²¹ We used unadjusted and adjusted Cox proportional hazard models to assess the effect of radiation therapy exposure on risk of breast reconstruction reoperation. Follow-up time started 10 months after mastectomy, and patients were censored at the time of reoperation, death, additional/delayed radiation therapy to the breast (anytime >300 days after index surgery for the unexposed or after 545 days for the exposed), loss to follow-up (defined as 1 year after the date of last contact for patients with no health care contact for >2 years before the end of the study window), or the end of follow-up (6 years after mastectomy). Adjusted analyses included patient age, institution teaching status, cancer diagnosis in past year, history of breast-conserving surgery with radiation, reconstruction type, and reoperation within the first 10 months of surgery. The proportional hazards assumption was evaluated for each covariate using previously described methods.²² Death was modeled as a competing risk in the primary analysis. Given that an additional operation is required after placement of a tissue expander, patients who initially received tissue expanders were permitted to have 1 operation during follow-up (before or after the 10-month threshold) that was not counted as an outcome or censoring event. For all analyses, reported *P* values are from 2-tailed tests where a value of <.05 was considered statistically significant. All analyses were performed using SAS EG version 7.15 (SAS Institute, Cary, NC).

Results

The study cohort included 2342 patients who underwent mastectomy with immediate reconstruction, of which 378 (16.1%) received adjuvant radiation therapy within 10 months of surgery. Within the overall cohort, median patient age was 49 years (interquartile range, 41-56) and 69.6% of patients had an implant-based reconstruction (implant only or flap with implant). Patients who received radiation therapy tended to be slightly younger, had fewer comorbid conditions (ie, lower expected resource utilization), and were much less likely to have had prior breast-conserving surgery and radiation (Table 1). Patients who received radiation were also much

Table 1 Baseline variables, overall and by radiation therapy status

Variable	Total (n = 2342)	No RT (n = 1964)	RT (n = 378)	SD	P value
Patient age*	49.0 (42.0-56.0)	49.0 (43.0-56.0)	47.5 (41.0-55.0)	0.15	.02
Rural residence	212 (9.1%)	182 (9.3%)	30 (7.9%)	0.05	.409
Neighborhood income [†]					.012
Quintile 1	265 (11.3%)	207 (10.5%)	58 (15.3%)	0.14	
Quintile 2	371 (15.8%)	309 (15.7%)	62 (16.4%)	0.02	
Quintile 3	418 (17.8%)	349 (17.8%)	69 (18.3%)	0.01	
Quintile 4	606 (25.9%)	513 (26.1%)	93 (24.6%)	0.03	
Quintile 5	676 (28.9%)	580 (29.5%)	96 (25.4%)	0.09	
Expected resource use					.009
Low utilization	612 (26.1%)	504 (25.7%)	108 (28.6%)	0.07	
Moderate utilization	1038 (44.3%)	854 (43.5%)	184 (48.7%)	0.10	
High utilization	692 (29.5%)	606 (30.9%)	86 (22.8%)	0.18	
History of lupus	51 (2.2%)	NR	≤5	0.13	.044
Previous lumpectomy	1177 (50.3%)	1093 (55.7%)	84 (22.2%)	0.73	<.001
History of BCT	466 (19.9%)	450 (22.9%)	16 (4.2%)	0.57	<.001
Type of reconstruction					.128
Flap	713 (30.4%)	610 (31.1%)	103 (27.2%)	0.08	
Implant	1403 (59.9%)	1159 (59.0%)	244 (64.6%)	0.11	
Implant and flap	226 (9.6%)	195 (9.9%)	31 (8.2%)	0.06	
Teaching institution	1482 (63.3%)	1253 (63.8%)	229 (60.6%)	0.07	.235
Surgeon experience*					
Mastectomy	20.0 (14.0-30.0)	20.0 (14.0-30.0)	20.0 (14.0-30.0)	0.03	.593
Reconstruction	15.0 (11.0-21.0)	15.0 (11.0-21.0)	14.0 (11.0-22.0)	0.01	.88

Abbreviations: BCT = breast-conserving therapy; NR = not reportable (owing to privacy requirements to prevent the recalculation of groups ≤5); RT = radiation therapy; SD = standardized difference.
* Median (interquartile range) years of experience.
[†] Missing data for 6 patients.

Table 2 Breast cancer diagnosis, stage, and time to surgery, overall and by radiation therapy status

Variable	Total (n = 2342)	No RT (n = 1964)	RT (n = 378)	SD	P value
Diagnosis within ≤1 y	1,255 (53.6%)	917 (46.7%)	338 (89.4%)	1.03	<.001
Diagnosis >1 y	372 (15.9%)	353 (18.0%)	19 (5.0%)	0.41	<.001
Cancer stage*					<.001
Stage 0	26 (2.1%)	NR	≤5	0.16	
Stage I	594 (47.3%)	530 (57.8%)	64 (18.9%)	0.87	
Stage II	387 (30.8%)	232 (25.3%)	155 (45.9%)	0.44	
Stage III	131 (10.4%)	24 (2.6%)	107 (31.7%)	0.84	
Stage IV	7 (0.6%)	≤5	≤5	0.01	
Stage not available	110 (8.8%)	102 (11.1%)	8 (2.4%)	0.35	
Time from diagnosis to mastectomy (d)*	83.0 (42.0-195.0)	85.0 (47.0-201.0)	71.5 (37.0-188.0)	0.14	.026

Abbreviations: NR = not reportable (owing to privacy requirements to prevent the recalculation of groups ≤5); RT = radiation therapy; SD = standardized difference.
* Limited to patients with a cancer diagnosis ≤1 year before mastectomy.

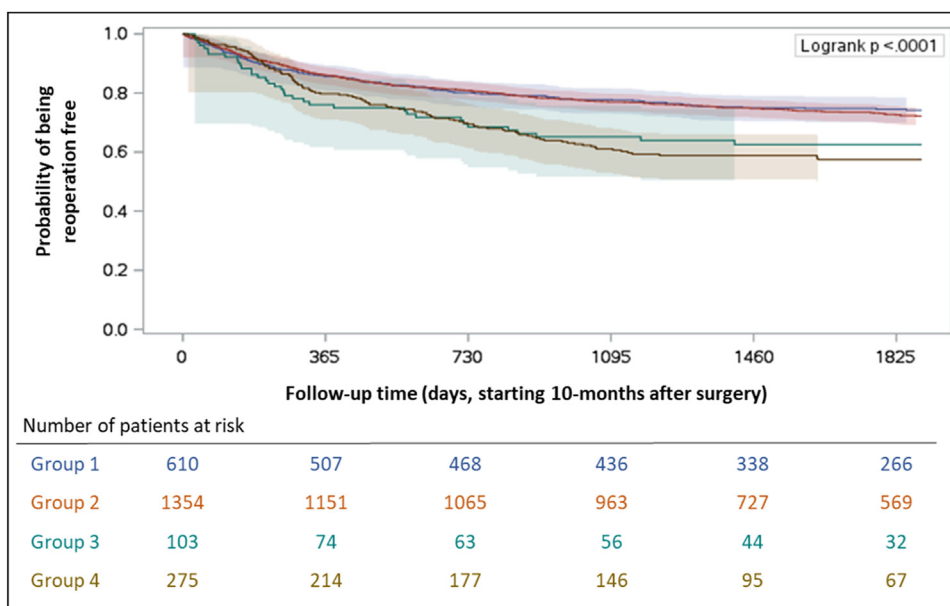


Figure 2 Kaplan-Meier 5-year survival curve: group 1 = flap without radiation therapy (RT), group 2 = implant without RT, group 3 = flap with RT, group 4 = implant with RT.

more likely to have a current breast cancer diagnosis (captured as a cancer diagnosis within 1 year of surgery; 89.4% vs 46.7%) and for that diagnosis to be associated with a higher cancer stage (stage 2 or higher: 78.1% vs 28.5%) (Table 2). Finally, patients who received adjuvant radiation therapy were significantly less likely to undergo an early reoperation for breast reconstruction within the first 10 months of the initial surgery (12.4% [n = 47] vs 30% [n = 590], $P < .001$), many of which were in patients who initially received a tissue expander.

Patients who received adjuvant radiation therapy within 10 months of surgery were significantly more likely to undergo reoperation for breast reconstruction during follow-up (57.1% vs 36.6%; odds ratio, 2.31; 95% confidence interval [CI], 1.85-2.89; $P < .001$). As can be seen in Fig. 2, which displays Kaplan-Meier curves for groups based on radiation status and type of initial reconstruction, patients with flap-based reconstructions and no radiation had the highest probability of being reoperation free, whereas radiated patients with implant-based reconstructions had the lowest probability of remaining reoperation free throughout the follow-up period.

Results from the Cox proportional hazards models also demonstrated that patients who received radiation were significantly more likely to undergo reoperation during follow-up, in both the unadjusted (hazard ratio [HR], 1.98; 95% CI, 1.69-2.31; $P < .0001$) and adjusted (HR, 1.82; 95% CI, 1.49-2.23; $P < .0001$) models (Table 3). Median time until censoring for patients in the radiation group was 513.5 days (IQR, 171-1586 days; 1.4 years), compared with 1389.5 days (IQR, 401-1890 days; 3.8 years) for patients who did not receive radiation.

Reoperation within the first 10 months of surgery was also significantly associated with further reoperation during the follow-up window (HR, 1.60; 95% CI, 1.35-1.89), whereas no significant associations were observed with respect to patient age, reconstruction type (implant vs flap), institution teaching status, current cancer diagnosis, or history of breast-conserving therapy.

Discussion

Results from this study demonstrate that adjuvant radiation therapy delivered after mastectomy with immediate breast reconstruction is associated with an increased risk of additional breast reconstruction surgery, even after adjusting for potential confounders, including type of reconstruction, and accounting for the second operation associated with tissue expanders (HR, 1.82; 95% CI, 1.49-2.23).

Overall, regardless of the type of reconstruction used, 27% of the patients in this study underwent a second operation within the first 10 months of surgery, and 40% did so later during follow-up (from 10 months to 6 years). In light of the large proportion of patients who require reoperation, it may be prudent for both surgeons and patients to plan beyond the initial operation in anticipation that additional procedures may be required, particularly if adjuvant radiation is needed and for those with implant-based reconstruction. While flap-based reconstructions may represent a more permanent option, they are also more of an up-front investment in terms of both a longer operative duration and a longer recovery period.

Table 3 Results from time-to-event analysis

Variable	HR	95% CI	P value
Radiation therapy (yes vs no)	1.82	1.49-2.23	<.0001
Age (per 10-y increase)	0.94	0.88-1.02	.133
Teaching institution (yes vs no)	1.03	0.87-1.21	.766
Current cancer diagnosis (yes vs no)	0.99	0.84-1.17	.887
History of breast-conserving therapy (yes vs no)	1.09	0.89-1.34	.393
Reconstruction type (implant vs flap)	1.01	0.85-1.21	.885
Early reoperation (yes vs no)	1.60	1.35-1.89	<.0001

Abbreviations: CI = confidence interval; HR = hazard ratio.

Of course, the risk of reoperation is only 1 factor in the myriad of considerations when choosing between flap and implant-based reconstructions, including physical characteristics of the breast, donor site, and personal preferences of the patient.

There may be approaches that reduce complications from radiation, especially in immediate implant-based procedures, which are increasingly being adopted by breast-reconstructive surgeons. One approach is to use tissue expanders in any patient who may need radiation, as opposed to permanent devices, which some research has shown to optimize esthetic results and minimize capsular contracture.²³ If a tissue expander is selected, ideally it should be inflated to near-full or full-volume when radiation is applied, as irradiated tissue is more difficult to expand.²⁴ Patient positioning and mitigating implant exposure while receiving the radiation therapy may also have a beneficial effect.²⁵ Novel emerging approaches, such as prepectoral implant-based reconstruction, where the implant is wrapped in acellular dermal matrix and placed in the subcutaneous pocket to help avoid pectoral capsular contracture, may emerge as options for minimizing radiation-related complications from immediate implant-based reconstruction given the lower reported rate of capsular contracture²⁶; however, there is currently limited experience with this approach and more research is needed.²⁷ Other novel adaptations to treatment include the delivery of postmastectomy radiation to the anterior aspect of the reconstruction, excluding the implant or tissue expander, such that radiation dosage is not delivered to the deep chest wall where recurrences are exceedingly rare,²⁸ thus avoiding circumferential full coverage of the reconstructive volume by the proscribed dose and resultant capsular contracture.

Early reoperation was found to be a predictor of later operation. This finding may reflect challenging reconstructions; for example, patients with acute ischemia to the reconstruction flap require revision of the vascular anastomoses, which can lead to fat necrosis requiring later revisions and fat grafting down the road. Alternatively, this could be related to infection or mastectomy flap

necrosis, requiring revision. Similarly, reoperations for acute hematoma in implant-based reconstructions may lead to infection and later explantation or contracture. Thus, early complications may, outside of the effects of radiation, lead to the need for further revisions, and this may simply reflect the complexity of achieving a cosmetically acceptable breast reconstruction in a single operation. This is true regardless of which type of reconstruction is used. Despite these potential challenges and perioperative complications, immediate breast reconstruction is felt to provide superior cosmetic results²⁹ in comparison to delayed reconstruction. Every effort should thus be made to minimize these complications while providing immediate reconstruction to eligible patients.

History of breast-conserving therapy was not found to be associated with increased risk of revision after adjusting for the other variables included in the model. Although findings from previous studies have been mixed, the weight of evidence suggests that history of radiation is associated with increased risk of complication and reconstruction failure, particularly in patients who undergo implant-based reconstruction.³⁰ While the focus of the current study was on postreconstruction radiation, the effect of prior radiation on breast reconstruction outcomes is an important area for further investigation.

Strengths and limitations

The current study provides population-level evidence for the rates of reoperations in a universal health care system where patient-borne cost does not factor in the decision to reoperate and can provide data for patient conversations and shared decision making. Conducting the study using large population-based health administrative databases allowed us to create a large, generalizable cohort of women who had undergone immediate breast reconstruction; however, administrative data have the potential for coding inaccuracies and are limited in terms of the type and quality of data that are available. Specifically, we were unable to reliability determine the

occurrence of chemotherapy or postmastectomy complications, such as infection and chronic wound-healing issues, both of which may increase risk of reconstruction failure. Moreover, data from Cancer Care Ontario (Ontario Health) has limited ability to capture breast cancer recurrence and cancer stage reflects stage at the time of diagnosis, not at the time of surgery. Taken together, our inability to capture and adjust for these variables likely resulted in residual confounding and should be considered when interpreting the findings from this study. It would also be ideal to follow patients prospectively, not only to collect patient-centered variables and outcomes but also to be able to capture the reason for reoperation, including planned 2-stage procedures and the occurrence of surgical complications. Given the data available, we were only able to determine that a second operation occurred, not if the operation was required due to radiation therapy–related complication versus any other reasons.

Conclusion

Results from this study demonstrate that adjuvant radiation therapy initiated after mastectomy with immediate breast reconstruction is associated with increased risk of future breast surgery. Planning beyond the initial operation in anticipation that additional procedures may be required is recommended, particularly for younger women, women who initially receive implant-based reconstructions, and women who may require radiation therapy. Further work to delineate the role of modified radiation delivery techniques and acellular dermal matrix use in reducing radiation-induced capsular contraction and reoperations is needed.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.adro.2022.101104](https://doi.org/10.1016/j.adro.2022.101104).

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