



Mesenchymal molecular subtype is an independent predictor of severe postoperative complications after primary debulking surgery for advanced ovarian cancer

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HIGHLIGHTS

- Molecular subtype is associated with severe complications after PDS.
- Patients with mesenchymal subtype are more likely to have severe complications after PDS.
- Molecular subtype is not associated 90-day mortality.

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ABSTRACT

Objective. To evaluate the contribution of molecular subtype to 30-day postoperative complications and 90-day mortality after primary debulking surgery (PDS) in advanced stage high-grade serous ovarian cancer (HGSOC).

Methods. Patients with stages III–IV HGSOC undergoing PDS from 1994 to 2011 with available molecular subtyping were included. Residual disease (RD) status was categorized as 0, 0.1–0.5, 0.6–1.0, or >1 cm. Surgical complexity scores were calculated as high, intermediate, or low as previously published. Postoperative complications were graded according to the modified Accordion classification 0–4 scale; severe was defined as grade ≥3. Molecular subtypes were derived from Agilent 4 × 44k tumor mRNA expression profiles and categorized as mesenchymal (MES) or non-mesenchymal (non-MES). Logistic regression modeling was used to assess associations.

Results. Of 329 patients, 68.7% were stage IIIC, 80.5% had RD ≤1 cm, 28.0% had MES subtype, and 19.5% had a grade 3–4 complication; 90-day mortality was 5.8%. In univariate analysis, patients with MES subtype were more likely to have severe complications compared to non-MES (31.5 vs. 14.8%; OR 2.66, 95% CI 1.51–4.69; $p < 0.001$). MES subtype remained an independent predictor of complications (adjusted OR 2.14, 95% CI 1.17–3.92; $p = 0.01$) in a multivariable model which included ASA score, preoperative albumin, and surgical complexity. There was no statistical difference in 90-day mortality in patients with MES compared to non-MES subtype (7.6 vs. 5.1%; OR 1.54, 95% CI 0.59–4.05; $p = 0.38$).

Conclusions. MES subtype is an independent predictor of severe postoperative morbidity and adds to the potential use of pre-operative molecular testing in planning primary treatment of patients with advanced ovarian cancer.

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1. Introduction

Primary debulking surgery (PDS) followed by adjuvant platinum-based chemotherapy is the standard of care in patients with

advanced-stage high-grade serous ovarian cancer (HGSOC) [1]. The Society of Gynecologic Oncology and the American Society of Clinical Oncology recommend that all new diagnoses undergo a primary clinical evaluation to determine if the patient is a candidate for PDS with acceptable risks and associated morbidity [2]. Previous studies, including our own, have identified several independent factors contributing to 30-day morbidity and 90-day mortality: increasing age, obesity, American Society of Anesthesiologists (ASA) score ≥ 3, preoperative albumin

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< 3.5 g/dL, stage, high surgical complexity score, and frailty [3–6]. Overall, >20% of patients experience severe postoperative complications after PDS [7–10]. Patients at high risk of postoperative complications may benefit from neoadjuvant chemotherapy followed by interval debulking surgery (NACT/IDS) [2,11]. Thus, it would be valuable to identify novel and objective risk factors that are associated with short-term morbidity and mortality to facilitate rational decision-making regarding PDS versus NACT/IDS.

Molecular subtypes based on gene expression describe defined subsets of HGSOE [12–14]. Patients with mesenchymal (MES) subtype are more likely to have upper abdominal and miliary disease [15]; higher surgical complexity scores [14]; and macroscopic residual disease [15]. Recently we described that patients with MES subtype are also more likely to have lower preoperative serum albumin levels [16]. While the mechanism of this association is unknown it suggests MES cancers may impact a patient's fitness for surgery. At minimum, patients with MES subtype are at higher risk of postoperative morbidity due to 1) higher disease burden, 2) requirement for higher complexity surgery, and 3) poor nutritional status. The latter is often poorly reflected in objective measures such as preoperative serum albumin level or performance status. Therefore, molecular profiling may offer a way to identify patients at higher risk of cancer-associated systemic changes that increase their risk of perioperative morbidity.

Our objective was to determine if there is an independent association between molecular subtype and 30-day postoperative complications or 90-day mortality after PDS in advanced HGSOE. This knowledge will add to the growing body of literature demonstrating the potential for molecular profiling in predicting outcomes of PDS [13–15,17].

2. Methods

The Mayo Clinic Institutional Review Board approved this single institution, retrospective study. Perioperative patient characteristics and surgical outcome variables were collected from prospectively maintained databases of patients undergoing PDS from 1994 to 2011. Inclusion criteria were high-grade (grade 2–4) serous or mixed serous histology, ovarian, fallopian, or primary peritoneal cancer, and operable stages III–IV with molecular subtyping. Patients with borderline tumors, those who were treated with NACT, and those without research consent or molecular profiling were excluded.

Intraperitoneal disease dissemination patterns among eligible patients were defined into three categories using our previously published criteria: pelvic disease, lower abdominal disease, and upper abdominal/miliary disease [15]. Four residual disease (RD) groups were defined, RD 0, RD 0.1–0.5 cm, RD 0.6–1.0 cm, RD >1 cm, based on the largest residual tumor diameter. Surgical complexity was assigned using previously published methods and classified as low, intermediate, or high complexity [3]. Postoperative complications were captured for the first 30 days after surgery and graded according to the modified Accordion classification 0–4 scale. Grade 3 complications were defined as “all complications requiring endoscopic or interventional radiologic procedures or reoperation as well as complications resulting in failure of one or more organs,” and grade 4 complications were defined as “death within 30 days” [18]. Date of death was used to capture the incidence of 90-day mortality.

Gene expression profiles were measured using Agilent Whole Human Genome 4 × 44K Expression Arrays. Expression data normalization and molecular subtype assignment was done as described in past publications [13,14]. Patients with molecular profiling data were assigned to one of four advanced stage HGSOE molecular subtypes: MES, immunoreactive (IMM), proliferative (PRO), or differentiated (DIFF). Since patients with IMM, PRO, and DIFF subtype have significantly better overall survival compared to MES subtype [15], we grouped them into one category (non-MES) for the statistical comparisons by molecular subtype.

Demographic, preoperative, and intraoperative characteristics were summarized. The primary outcome measures were presence of severe (Accordion grade 3–4) complications within 30 days after surgery and 90-day mortality. Univariate and multivariable logistic regression models were fit to evaluate the association between molecular subtype and each binary outcome. Associations were summarized by calculating the odds ratio (OR) and corresponding 95% confidence interval (CI). Variables considered in the modeling were based on previously established factors associated with postoperative morbidity and mortality (age at surgery, body mass index (BMI)), ASA score, preoperative albumin level, surgical complexity, and International Federation of Gynecology and Obstetrics (FIGO) stage [5] and the two new variables of interest (intraperitoneal dissemination pattern and molecular subtype). Surgical complexity was used instead of RD in this model because it is a better predictor of postoperative complications. Multivariable

Table 1
Patient demographics and perioperative characteristics.

Characteristic	N = 329
Age at surgery (years), mean (SD)	63.6 (11.3)
BMI (kg/m ²), mean (SD)	28.3 (6.2)
BMI (kg/m ²), N (%)	
<25.0	93 (28.3)
25.0–29.9	99 (30.1)
30.0–39.9	74 (22.5)
≥40	15 (4.6)
Unknown	48 (14.6)
ASA score, N (%)	
<3	170 (51.7)
≥3	159 (48.3)
Primary organ site, N (%)	
Ovarian	306 (93.0)
Peritoneum	20 (6.1)
Fallopian tube	3 (0.9)
Preoperative albumin, N (%)	
≥3.5 g/dL	140 (42.6)
<3.5 g/dL	39 (11.9)
Not available	150 (45.6)
FIGO stage, N (%)	
IIIA/B	24 (7.3)
IIIC	226 (68.7)
IV	79 (24.0)
FIGO grade, N (%)	
2	7 (2.1)
3	228 (69.3)
4	94 (28.6)
Histology, N (%)	
True serous	311 (94.5)
Mixed serous	18 (5.5)
Ascites, N (%)	
No	76 (23.1)
Yes	207 (62.9)
Unknown	46 (14.0)
Residual disease (cm), N (%)	
0	98 (29.8)
0.1–0.5	131 (39.8)
0.6–1.0	36 (10.9)
>1.0	55 (16.7)
Unknown	9 (2.7)
Surgical complexity, N (%)	
Low	66 (20.1)
Intermediate	154 (46.8)
High	109 (33.1)
Molecular subtype, N (%)	
Proliferative	90 (27.4)
Differentiated	72 (21.9)
Mesenchymal	92 (28.0)
Immunoreactive	75 (22.8)
Intraperitoneal dissemination pattern, N (%)	
Pelvic	26 (7.9)
Lower abdominal	47 (14.3)
Upper abdominal/miliary	256 (77.8)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.

models were fit using stepwise and backward variable selection methods; variables in the adjusted model with a p value < 0.05 were retained in the final multivariable model. Statistical analysis was performed using the SAS version 9.4 software package (SAS Institute, Inc.; Cary, NC). All calculated p values were two-sided, and p values < 0.05 were considered statistically significant.

3. Results

Between 1994 and 2011, 741 patients with stage III or IV HGSO underwrote PDS with curative intent. Among these patients, 329 had molecular profiling performed (randomly selected) and an Accordion complication grade. This subset of patients was representative of the full cohort in terms of patient and disease characteristics, except a higher proportion of patients with molecular profiling were primary ovarian and stage IV. Among the 329 patients selected for this current study, the mean age at diagnosis was 63.6 years, and the majority of patients had stage IIIC disease (68.7%) and 265 (80.5%) had cytoreduction to ≤ 1 cm, including 98 (29.8%) with a complete cytoreduction. Patient and tumor characteristics are summarized in Table 1.

A total of 64 (19.5%) of patients went on to have a severe postoperative complication, of which 56 (17.0%) were grade 3 and 8 (2.4%) were grade 4 (death within 30 days) (Table 2). As expected, in univariable analysis the following factors were important predictors of severe postoperative complications: age (OR per 10-year increase 1.31, 95% CI 1.02–1.69), ASA score ≥ 3 (OR 2.22, 95% CI 1.26–3.91), preoperative albumin < 3.5 g/dL (OR 2.91, 95% CI 1.36–6.25), and surgical complexity (high versus low; OR 3.20, 95% CI 1.32–7.79). In addition, MES subtype was associated with the development of a severe postoperative complication compared to non-MES (31.5 vs. 14.8%; OR 2.66, 95% CI 1.51–4.69; $p < 0.001$) but intraperitoneal dissemination pattern was not ($p = 0.57$). Patients with MES subtype were more likely to have ASA score ≥ 3 ($p = 0.06$), primary peritoneal cancer ($p = 0.002$), preoperative albumin < 3.5 g/dL ($p = 0.008$), FIGO stage IV ($p = 0.005$), and

macroscopic RD ($p < 0.001$) compared to patients with non-MES subtype (Table 3). Despite this, MES subtype remained an important predictor of severe postoperative complications (adjusted OR 2.14, 95% CI 1.17–3.92; $p = 0.01$) in a multivariable model including ASA score, preoperative albumin, and surgical complexity. These results suggest that patients with MES subtype are more likely to have severe morbidity and mortality within 30 days after PDS.

We also sought to measure the association between clinically-relevant variables, molecular subtype, intraperitoneal disease dissemination patterns, and 90-day mortality. A total of 19 (5.8%) patients died within 90 days after surgery. As expected, in univariate analysis the following factors were important predictors of 90-day mortality: older age, BMI ≥ 40 kg/m², ASA score ≥ 3 , and preoperative albumin < 3.5 g/dL (Table 4). MES subtype was not associated with 90-day mortality (MES vs. non-MES: 7.6 vs. 5.1%; OR 1.54, 95% CI 0.59–4.05; $p = 0.38$) but power was limited due to the small number of events. Among the 321 patients that didn't die within 30 days of surgery, 10.7% (6/56) of the patients with a grade 3 complication died within 90 days compared to 1.9% (5/265) of the remaining patients (OR 6.24, 95% CI 1.83–21.24; $p = 0.003$).

4. Discussion

Previous prediction models for postoperative complications in ovarian cancer have not investigated molecular subtype as a contributor to the risk of postoperative morbidity [5]. Given the potential impact of tumor biology on host immune response and performance status, it seems plausible that the molecular subtype could impact perioperative outcomes in ovarian cancer. In this study, we show that MES subtype is an independent predictor of severe postoperative complications. These results suggest that molecular subtype may have utility in predicting the risk of surgery in patients with advanced ovarian cancer.

We previously published a risk-prediction model of severe postoperative complications after PDS for advanced ovarian cancer which

Table 2

Logistic regression modeling for the odds of a severe (Accordion grade 3+) postoperative complication within 30 days after surgery.

Characteristic	No. (%) with outcome	Univariable analysis		Multivariable analysis	
		Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Age at surgery (years)	–	1.31 (1.02, 1.69)*	0.04		
BMI (kg/m ²)					
<25.0 (N = 93)	15 (16.1)	Reference	0.33		
25.0–29.9 (N = 99)	20 (20.2)	1.32 (0.63, 2.76)			
30.0–39.9 (N = 74)	13 (17.6)	1.11 (0.49, 2.50)			
≥ 40 (N = 15)	6 (40.0)	3.47 (1.07, 11.19)			
Unknown (N = 48)	10 (20.8)	1.37 (0.56, 3.33)			
ASA score					
<3 (N = 170)	23 (13.5)	Reference	0.006	Reference	0.02
≥ 3 (N = 159)	41 (25.8)	2.22 (1.26, 3.91)		2.01 (1.11, 3.63)	
Preoperative albumin					
≥ 3.5 g/dL (N = 140)	27 (19.3)	Reference	0.001	Reference	0.02
<3.5 g/dL (N = 39)	16 (41.0)	2.91 (1.36, 6.25)		2.32 (1.03, 5.23)	
Not available (N = 150)	21 (14.0)	0.68 (0.37, 1.27)		0.68 (0.36, 1.30)	
FIGO stage					
IIIA/B (N = 24)	1 (4.2)	Reference	0.07		
IIIC (N = 226)	42 (18.6)	5.25 (0.69, 39.96)			
IV (N = 79)	21 (26.6)	8.33 (1.06, 65.55)			
Surgical complexity					
Low (N = 66)	7 (10.6)	Reference	0.02	Reference	0.03
Intermediate (N = 154)	27 (17.5)	1.79 (0.74, 4.35)		1.97 (0.78, 4.93)	
High (N = 109)	30 (27.5)	3.20 (1.32, 7.79)		3.22 (1.28, 8.12)	
Molecular subtype					
Non-mesenchymal (N = 237)	35 (14.8)	Reference	<0.001	Reference	0.01
Mesenchymal (N = 92)	29 (31.5)	2.66 (1.51, 4.69)		2.14 (1.17, 3.92)	
Intraperitoneal dissemination pattern					
Pelvic (N = 26)	4 (15.4)	Reference	0.57		
Lower abdominal (N = 47)	7 (14.9)	0.96 (0.25, 3.65)			
Upper abdominal/miliary (N = 256)	53 (20.7)	1.44 (0.47, 4.35)			

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; OR, odds ratio.

* Odds ratio per 10-year increase in age.

Table 3
Comparison of patient demographics and perioperative characteristics by molecular subtype.

Characteristic	Non-mesenchymal	Mesenchymal	p [†]
	N = 237	N = 92	
Age at surgery (years), mean (SD)	63.3 (11.3)	64.2 (11.4)	0.27
BMI (kg/m ²), mean (SD)	28.3 (6.1)	28.4 (6.6)	0.89
BMI (kg/m ²), N (%)			
<25.0	67 (28.3)	26 (28.3)	0.83
25.0–29.9	70 (29.5)	29 (31.5)	
30.0–39.9	57 (24.1)	17 (18.5)	
≥40	10 (4.2)	5 (5.4)	
Unknown	33 (13.9)	15 (16.3)	
ASA score, N (%)			
<3	130 (54.9)	40 (43.5)	0.06
≥3	107 (45.1)	52 (56.5)	
Primary organ site, N (%)			
Ovarian	225 (94.9)	81 (88.0)	0.002
Peritoneum	9 (3.8)	11 (12.0)	
Fallopian tube	3 (1.3)	0 (0.0)	
Preoperative albumin, N (%)			
≥3.5 g/dL	106 (44.7)	34 (37.0)	0.008
<3.5 g/dL	20 (8.4)	19 (20.7)	
Not available	111 (46.8)	39 (42.4)	
FIGO stage, N (%)			
IIIA/B	23 (9.7)	1 (1.1)	0.005
IIIC	165 (69.6)	61 (66.3)	
IV	49 (20.7)	30 (32.6)	
FIGO grade, N (%)			
2	7 (3.0)	0 (0.0)	0.07
3	157 (66.2)	71 (77.2)	
4	73 (30.8)	21 (22.8)	
Histology, N (%)			
True serous	224 (94.5)	87 (94.6)	0.99
Mixed serous	13 (5.5)	5 (5.4)	
Ascites, N (%)			
No	59 (24.9)	17 (18.5)	0.29
Yes	143 (60.3)	64 (69.6)	
Unknown	35 (14.8)	11 (12.0)	
Residual disease (cm), N (%)			
0	87 (36.7)	11 (12.0)	<0.001
0.1–0.5	87 (36.7)	44 (47.8)	
0.6–1.0	23 (9.7)	13 (14.1)	
>1.0	35 (14.8)	20 (21.7)	
Unknown	5 (2.1)	4 (4.3)	
Surgical complexity, N (%)			
Low	49 (20.7)	17 (18.5)	0.35
Intermediate	115 (48.5)	39 (42.4)	
High	73 (30.8)	36 (39.1)	
Intraperitoneal dissemination pattern, N (%)			
Pelvic	23 (9.7)	3 (3.3)	<0.001
Lower abdominal	43 (18.1)	4 (4.3)	
Upper abdominal/miliary	171 (72.2)	85 (92.4)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.

[†] Wilcoxon rank-sum p value reported for continuous variables and chi-square p value reported for categorical variables.

included preoperative albumin, ASA score, and surgical complexity [5]. By introducing molecular subtype into the existing model, we have identified a novel and objective risk factor associated with perioperative morbidity. Our data shows that patients with MES subtype are more than twice as likely to have a severe postoperative complication. Previously we showed that patients with MES subtype are also more likely to have upper abdominal disease and macroscopic RD [15,17]. The need for more complex surgery creates a dilemma for patients with aggressive tumor biology. This builds upon previous work that should be useful in triage of new ovarian cancer patients. An ideal prediction model would encompass resectability of disease, impact on survival, and risks of short term perioperative complications. Future studies should strive to develop a model which includes clinical, radiographic, and molecular risk factors. This would better assign patients into predicted outcome groups defined by surgical outcome (RD0/RD1/RD2) and severe surgical complications. For example, for a patient who we predict can

Table 4
Univariate logistic regression modeling for the odds of 90-day mortality.

Characteristic	No. (%) with outcome	Unadjusted OR (95% CI)	p
Age at surgery (years) ^a	–	1.89 (1.18, 3.04)	0.009
BMI (kg/m ²)			
<25.0 (N = 93)	5 (5.4)	Reference	0.01
25.0–29.9 (N = 99)	3 (3.0)	0.55 (0.13, 2.37)	
30.0–39.9 (N = 74)	2 (2.7)	0.49 (0.09, 2.60)	
≥40 (N = 15)	4 (26.7)	6.40 (1.49, 27.46)	
Unknown (N = 48)	5 (10.4)	2.05 (0.56, 7.45)	
ASA score			
<3 (N = 170)	3 (1.8)	Reference	0.004
≥3 (N = 159)	16 (10.1)	6.23 (1.78, 21.81)	
Preoperative albumin			
≥3.5 g/dL (N = 140)	7 (5.0)	Reference	0.006
<3.5 g/dL (N = 39)	7 (17.9)	4.16 (1.36, 12.69)	
Not available (N = 150)	5 (3.3)	0.66 (0.20, 2.11)	
FIGO stage			
IIIA/B (N = 24)	1 (4.2)	Reference	0.06
IIIC (N = 226)	9 (4.0)	0.95 (0.12, 7.87)	
IV (N = 79)	9 (11.4)	2.96 (0.36, 24.61)	
Surgical complexity			
Low (N = 66)	4 (6.1)	Reference	0.80
Intermediate (N = 154)	10 (6.5)	1.08 (0.33, 3.56)	
High (N = 109)	5 (4.6)	0.75 (0.19, 2.88)	
Molecular subtype			
Non-mesenchymal (N = 237)	12 (5.1)	Reference	0.38
Mesenchymal (N = 92)	7 (7.6)	1.54 (0.59, 4.05)	
Intraperitoneal dissemination pattern			
Pelvic (N = 26)	1 (3.8)	Reference	0.79
Lower abdominal (N = 47)	2 (4.3)	1.11 (0.10, 12.87)	
Upper abdominal/miliary (N = 256)	16 (6.3)	1.67 (0.21, 13.10)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; OR, odds ratio.

^a Odds ratio per 10-year increase in age.

be resected to RD1, but not RD0, is her risk of complication low enough to proceed with PDS or is her risk of complication so high that PDS should be avoided? This is important to assist providers in personalizing treatment plans.

Molecular subtype independently predicts morbidity, even when adjusted for surgical complexity and pre-operative serum albumin; factors which have historically been key drivers of post-operative outcomes. In fact, even though patients with MES subtype are more likely to have pre-operative serum albumin levels ≤ 3.5 g/dL [16], molecular subtype remained an independent predictor of complications. This suggests that molecular subtype may be acting through other mechanisms to reduce the ability of the patient to recover. Although the mechanisms are not clear, future studies should investigate associations between molecular subtype and frailty: such research may offer insight into targeted interventions to improve tumor-associated deficits.

The major strength of this study is the use of a large single institution database with detailed operative reports, outcomes data, and molecular profiling. Our multivariable model included clinically significant variables widely accepted to be associated with severe postoperative complications [5]. The major limitation is that these surgeries were over a large period of time (1994–2011) and rates of complete cytoreduction varied across these years [7]. They also predated enhanced recovery and intervention bundles that reduced the rates of surgical site infections, anastomotic leaks, and blood transfusions [19–22]. These factors could contribute to differences in surgical complexity and postoperative complications over time [7].

We identified molecular subtype as a novel and objective risk factor for postoperative morbidity after PDS for advanced HGSO. Our results add to the growing body of literature that has shown that molecular profiles are an important predictor of dissemination patterns, resectability of disease, and overall survival in patients undergoing PDS [13–15,17]. Clearly, the utility of incorporating preoperative molecular subtyping is limited by the complexity of performing molecular

analyses [13] and absence of other external validation. Molecular assays are commonly performed to predict prognosis and response to therapy in patients with breast cancer [23,24]. The American Society of Clinical Oncology supports the use of biomarkers to guide decisions on adjuvant systemic therapy for patients with early-stage invasive breast cancer [25]. As ovarian cancer research continues to evolve, investigators should continue to explore the potential expanded role of tumor biology in predicting response to therapy (surgical and medical) and tumor host response in our patients. The most logical next step would be for other large centers or a multicenter collaboration to retrospectively confirm these findings. If externally validated then adding this variable to risk prediction models would be reasonable. This knowledge may one day be coupled with clinical predictors to personalize treatment approaches to maximize oncologic outcomes and minimize perioperative morbidity in the primary treatment of advanced ovarian cancer.

Conflicts of interest

None of the authors have any conflicts of interest to declare.

Authors' contribution

Conceived and designed the study: Diogo Torres, William A. Cliby, Chen Wang.

Collected the data: Diogo Torres, Chen Wang, Amanika Kumar, Carrie L. Langstraat.

Contributed data or analysis tools: Chen Wang, Carrie L. Langstraat, Jamie N. Bakkum-Gamez, Amanika Kumar.

Performed the analysis: Chen Wang, Amy L. Weaver, Michaela E. McGree.

Wrote the paper: Diogo Torres, William A. Cliby.

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